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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C12N 15/12, 15/63, 15/64
C12N 5/10, C07K 13/00
A01N 33/00, A61K 37/00

A1

(11) International Publication Number: WO 92/17585

(43) International Publication Date: 15 October 1992 (15.10.92)

(21) International Application Number: PCT/US92/02741

(22) International Filing Date: 6 April 1992 (06.04.92)

(30) Priority data:
681,880 5 April 1991 (05.04.91) US

(60) Parent Application or Grant
(63) Related by Continuation
US 681,880 (CIP)
Filed on 5 April 1991 (05.04.91)

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: ODORANT RECEPTORS ANS USES THEREOF

(57) Abstract

The invention provides an isolated nucleic acid, e.g. cDNA encoding an odorant receptor. The invention further provides expression vectors containing such nucleic acid. Also provided is a purified protein encoding an odorant receptor, with the aforementioned expression vectors and the resulting transformed cell. The invention also provides methods of identifying odorant ligands and of identifying odorant receptors. The invention further provides methods of developing fragrances, of identifying appetite suppressant compounds, of controlling appetite, of controlling pest populations, of promoting and inhibiting fertility, and of detecting odors.

USSN # 09/847,102
Docket # 220002062900

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ODORANT RECEPTORS AND USES THEREOF

Background of th Invention

This application is a continuation-in-part of U.S. Serial No.681,880, filed April 5, 1991, the contents of which are hereby incorporated by reference.

Throughout this application, various publications are referenced by Arabic numerals within parentheses. Full citations for these publications may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

In vertebrate sensory systems, peripheral neurons respond to environmental stimuli and transmit these signals to higher sensory centers in the brain where they are processed to allow the discrimination of complex sensory information. The delineation of the peripheral mechanisms by which environmental stimuli are transduced into neural information can provide insight into the logic underlying sensory processing. Our understanding of color vision, for example, emerged only after the observation that the discrimination of hue results from the blending of information from only three classes of photoreceptors (1, 2, 3, 4). The basic logic underlying olfactory sensory perception, however, has remained elusive. Mammals possess an olfactory system of enormous discriminatory power (5, 6). Humans, for example, are thought to be capable of distinguishing among thousands of distinct odors. The specificity of odor recognition is emphasized by the observation that subtle alterations in the molecular structure of an odorant can lead to profound

changes in perceived odor.

The detection of chemically distinct odorant presumably results from the association of odorous ligands with specific receptors on olfactory neurons which reside in a specialized epithelium in the nose. Since these receptors have not been identified, it has been difficult to determine how odor discrimination might be achieved. It is possible that olfaction, by analogy with color vision, involves only a few odor receptors, each capable of interaction with multiple odorant molecules. Alternatively, the sense of smell may involve a large number of distinct receptors each capable of associating with one or a small number of odorant. In either case, the brain must distinguish which receptors or which neurons have been activated to allow the discrimination between different odorant stimuli. Insight into the mechanisms underlying olfactory perception is likeLY to depend upon the isolation of the odorant receptors, and the characterization of their diversity, specificity, and patterns of expression.

The primary events in odor detection occur in a specialized olfactory neuroepithelium located in the posterior recesses of the nasal cavity. Three cell types dominate this epithelium (Figure 1A): the olfactory sensory neuron, the sustentacular or supporting cell, and the basal cell which is a stem cell that generates olfactory neurons throughout life (7, 8). The olfactory sensory neuron is bipolar: a dendritic process extends to the mucosal surface where it gives rise to a number of specialized cilia which provide an extensive, receptive surface for the interaction of odors with olfactory sensory neurons. The olfactory neuron also gives rise to an axon which projects to the olfactory bulb of the brain, the first relay in the olfactory system. The axons of the olfactory bulb neurons, in turn, project to

subcortical and cortical regions where higher level processing of olfactory information allows the discrimination of odors by the brain.

The initial events in odor discrimination are thought to involve the association of odors with specific receptors on the cilia of olfactory neurons. Selective removal of the cilia results in the loss of olfactory response (9). Moreover, in fish, whose olfactory system senses amino acids as odors, the specific binding of amino acids to isolated cilia has been demonstrated (10, 11). The cilia are also the site of olfactory signal transduction. Exposure of isolated cilia from rat olfactory epithelium to numerous odorant leads to the rapid stimulation of adenylyl cyclase and elevations in cyclic AMP (an elevation in IP3 in response to one odorant has also been observed) (12, 13, 14, 15). The activation of adenylyl cyclase is dependent on the presence of GTP and is therefore likely to be mediated by receptor-coupled GTP binding proteins (G-proteins) (16). Elevations in cyclic AMP, in turn, are thought to elicit depolarization of olfactory neurons by direct activation of a cyclic nucleotide-gated, cation permeable channel (17, 18). This channel is opened upon binding of cyclic nucleotides to its cytoplasmic domain, and can therefore transduce changes in intracellular levels of cyclic AMP into alterations in the membrane potential.

These observations suggest a pathway for olfactory signal transduction (Figure 1B) in which the binding of odors to specific surface receptors activates specific G-proteins. The G-proteins then initiate a cascade of intracellular signalling events leading to the generation of an action potential which is propagated along the olfactory sensory axon to the brain. A number of neurotransmitter and hormone receptors which transduce intracellular signals by

activation of specific G-proteins have been identified. Gene cloning has demonstrated that each of these receptors is a member of a large superfamily of surface receptors which traverse the membrane seven times (19, 20). The pathway of olfactory signal transduction (Figure 1B) predicts that the odorant receptors might also be members of this superfamily of receptor proteins. The detection of odors in the periphery is therefore likely to involve signalling mechanisms shared by other hormone or neurotransmitter systems, but the vast discriminatory power of the olfactory system will require higher order neural processing to permit the perception of individual odors. This invention address the problem of olfactory perception at a molecular level. Eighteen different members of an extremely large multigene family have been cloned and characterized which encodes seven transmembrane domain proteins whose expression is restricted to the olfactory epithelium. The members of this novel gene family encode the individual odorant receptors.

SUMMARY OF THE INVENTION

The invention provides an isolated nucleic acid, e.g. a DNA and cDNA molecule, encoding an odorant receptor. The invention further provides expression vectors containing such nucleic acid. Also provided by the invention is a purified protein encoding an odorant receptor. The invention further provides a method of transforming cells which comprises transfecting a suitable host cell with a suitable expression vector containing the nucleic acid encoding the odorant receptor.

The invention also provides methods of identifying odorant ligands and of identifying odorant receptors. The invention further provides methods of developing fragrances, of identifying appetite suppressant compounds, of controlling appetite. The invention also provides methods of controlling insect and other animal populations. The invention additionally provides a method of detecting odors such as the vapors emanating from Cocaine, Marijuana, Heroin, Hashish, Angel Dust, gasoline, decayed human flesh, alcohol, gun powder explosives, plastic explosives, firearms, poisonous or harmful smoke, or natural gas.

Description of the Figures

Figure 1. The Olfactory Neuroepithelium and a Pathway for Olfactory Signal Transduction. A. The Olfactory Neuroepithelium. The initial event in odor perception occurs in the nasal cavity in a specialized neuroepithelium which is diagrammed here. Odors are believed to interact with specific receptors on the cilia of olfactory sensory neurons. The signal generated by these initial binding events are propagated by olfactory neuron axons to the olfactory bulb. B. A Pathway of Olfactory Signal Transduction. In this scheme, the binding of an odorant molecule to an odor-specific transmembrane receptor leads to the interaction of the receptor with a GTP-binding protein ($G_{S[olf]}$). This interaction, in turn, leads to the release of the GTP-coupled α-subunit of the G-protein, which then stimulates adenylyl cyclase to produce elevated levels of cAMP. The increase in cAMP opens nucleotide-gated cation channels, thus causing an alteration in membrane potential.

Figure 2. A PCR Amplification Product Containing Multiple Species of DNA. cDNA prepared from olfactory epithelium RNA was subjected to PCR amplification with a series of different primer oligonucleotides and the DNA products of appropriate size were isolated, further amplified by PCR, and size fractionated on agarose gels (A) (For details, see text). Each of these semipurified PCR products was digested with the restriction enzyme, Hinf I, and analyzed by agarose gel electrophoresis. Lanes marked "M" contain size markers of 23.1, 9.4, 5.6, 4.4, 2.3, 2.0, 1.35, 1.08, 0.87, 0.60, 0.31, 0.28, 0.23, 0.19, 0.12 and 0.07kb. (B). Twenty-two of the 64 PCR products that were isolated and digested with Hinf I are shown here. Digestion of one of these, PCR 13, yielded a large number of fragments whose sizes summed to a value much greater than that of the undigested PCR 13

DNA, indicating that PCR 13 might contain multiple species of DNA which are representatives of a multigene family.

Figure 3. Northern Blot Analysis with a Mixture of Twenty Probes. One μg of polyA+ RNA isolated from rat olfactory epithelium, brain, or spleen was size-fractionated in formaldehyde agarose, blotted onto a nylon membrane, and hybridized with a ^{32}P-labeled mixture of segments of 20 cDNA clones. The DNA segments were obtained by PCR using primers homologous to transmembrane domains 2 and 7.

Figure 4. The Protein Sequences Encoded by Ten Divergent cDNA Clones. Ten divergent cDNA clones were subjected to DNA sequence analyses and the protein sequence encoded by each was determined. Amino acid residues which are conserved in 60% or more of the proteins are shaded. The presence of seven hydrophobic domains (I-VII), as well as short conserved motifs shared with other members of the superfamily, demonstrate that these proteins belong to the seven transmembrane domain protein superfamily. Motifs conserved among members of the superfamily and the family of olfactory proteins include the GN in TM1 (transmembrane domain 1), the central W of TM4, the Y near the C-terminal end of TM5, and the NP in TM7. In addition, the DRY motif C-terminal to TM3 is common to many members of the G-protein-coupled superfamily. However, all of the proteins shown here share sequence motifs not found in other members of this superfamily and are clearly members of a novel family of proteins.

Figure 5. Positions of Greatest Variability in the Olfactory Protein Family. In this diagram, the protein encoded by cDNA clone I15 is shown traversing the plasma membrane seven times with its N-terminus located extracellularly, and its C-terminus intracellularly. The

vertical cylinders delineate the seven putative α-helices spanning the membrane. Positions at which 60% or more of the 10 clones shown in Figure 4 share the same residue as I15 are shown as white balls. More variable residues are shown as black balls. The high degree of variability encountered in transmembrane domains III, IV, and V is evident in this schematic.

Figure 6. The Presence of Subfamilies in a Divergent Multigene Family. Partial nucleotide sequences and deduced protein sequences were obtained for 18 different cDNA clones. Transmembrane domain V along with the flanking loop sequences, including the entire cytoplasmic loop between transmembrane domains V and VI, are shown here for each protein. Amino acid residues found in 60% or more of the clones in a given position are shaded (A). This region of the olfactory proteins (particularly transmembrane domain V) appears to be highly variable (see Figure 4). These proteins, however, can be grouped into subfamilies (B,C,D) in which the individual subfamily members share considerable homology in this divergent region of the protein.

Figure 7. Southern Blot Analyses with Non-crosshybridizing Fragments of Divergent cDNAs. Five μg of rat liver DNA was digested with Eco RI (A) or Hind III (B), electrophoresed in 0.75% agarose, blotted onto a nylon membrane, and hybridized to the ^{32}P-labeled probes indicated. The probes used were PCR-generated fragments of: 1, clone F9 (identical to F12 in Figure 4); 2, F5; 3, F6; 4, I3; 5, I7; 6, I14; or 7, I15. The lane labeled "1-7" was hybridized to a mixture of the seven probes. The probes used showed either no crosshybridization or only trace crosshybridization with one another. The size markers on the left correspond to the four blots on the left (1-4) whereas the marker positions noted on the right correspond to the four blots on the right

(5-7, "1-7").

Figure 8. <u>Northern Blot Analysis with a Mix of Seven Divergent Clones</u>. One µg of polyA+ RNA from each of the tissues shown was size-fractionated, blotted onto a nylon membrane, and hybridized with a ^{32}P-labeled mixture of segments of seven divergent cDNA clones (see Legend to Figure 7).

Figure 9. The amino acid and nucleic acid sequence of clone F3.

Figure 10. The amino acid and nucleic acid sequence of clone F5.

Figure 11. The amino acid and nucleic acid sequence of clone F6.

Figure 12. The amino acid and nucleic acid sequence of clone F12.

Figure 13. The amino acid and nucleic acid sequence of clone I3.

Figure 14. The amino acid and nucleic acid sequence of clone I7.

Figure 15. The amino acid and nucleic acid sequence of clone I8.

Figure 16. The amino acid and nucleic acid sequence of clone I9.

Figure 17. The amino acid and nucleic acid sequence of clone I14.

Figure 18. The amino acid and nucleic acid sequence of clone I15.

Figure 19. The amino acid and nucleic acid sequence of human clone H5.

Figure 20. The amino acid and nucleic acid sequence of clone J1, where the reading frame starts at nucleotide position 2.

Figure 21. The amino acid and nucleic acid sequence of clone J2.

Figure 22. The amino acid and nucleic acid sequence of clone J4, where the reading frame starts at nucleotide position 2.

Figure 23. The amino acid and nucleic acid sequence of clone J7, where the reading frame starts at nucleotide position 2.

Figure 24. The amino acid and nucleic acid sequence of clone J8, where the reading frame starts at nucleotide positon 2.

Figure 25. The amino acid and nucleic acid sequence of clone J11.

Figure 26. The amino acid and nucleic acid sequence of clone J14, where the reading frame starts at nucleotide position 2.

Figure 27. The amino acid and nucleic acid sequence of clone J15, where the reading frame starts at nucleotide psition 2.

Figure 28. The amino acid and nucleic acid sequence of clone J16, where the reading frame starts at nucleotide position 2.

Figure 29. The amino acid and nucleic acid sequence of clone J17, where the reading frame starts at nucleotide position 2.

Figure 30. The amino acid and nucleic acid sequence of clone J19, where the reading frame starts at nucleotide position 2.

Figure 31. The amino acid and nucleic acid sequence of clone J20, where the reading frame starts at nucleotide position 2.

Figure 32. SOUTHERN BLOT: Five micrograms of DNA isolated from 1. Human placenta, 2. NCI-H-1011 neuroblastoma cells, or 3. CHP 134 neuroblastoma cells were treated with the restriction enzyme A. Eco RI, B. Hind III, C. Bam HI, or D. Pst I, and then electrophoresed on an agarose gel and blotted onto a nylon membrane. The blotted DNA was hybridized to the 32P-labeled H3/H5 sequence. An autoradiograph of the hybridized blot is shown with the sizes of co-electrophoresed size markers noted in kilobases.

Detailed Description of the Invention

The invention provides an isolated nucleic acid, e.g. a DNA or cDNA molecule, encoding an odorant receptor. Such a receptor is a receptor which binds an odorant ligand and include but not limited to pheromone receptors. An odorant ligand may include, but is not limited to, molecules which interact with the olfactory sensory neuron, molecules which interact with the olfactory cilia, pheromones, and molecules which interact with structures within the vomeronasal organ.

The invention specifically provides the isolated cDNAs encoding odorant receptors the sequences of which are shown in Figures 9-31. The nucleic acid is most typically a cDNA and encodes an insect, a vertebrate, a fish or a mammalian odorant receptor. The mammalian odorant receptor is preferably a human, rat, mouse or dog receptor. In an embodiment, human odorant receptor cDNA sequence and the correspondent protein is isolated (Figure 19).

In another embodiment, phermone receptors are isolated and shown as clones J1, J2, J4, J7, J8, J11, J14, J15, J16, J17, J19 and J20 (Figures 20-31).

The invention further provides expression vectors containing cDNA which encodes odorant receptors. Such expression vectors are well known in the art and include in addition to the nucleic acid the elements necessary for replication and expression in a suitable hosts. Suitable hosts are well known in the art and include without limitation bacterial hosts such as E. coli, animal hosts such as CHO cells, insect cells, yeast cells and like.

The invention also provides purified proteins encoding odorant receptors. Such proteins may be prepared by

expression of the forementioned expression vectors in suitable host cells and recovery and purification of the receptors using methods well known in the art. Examples of such proteins include those having the amino acid sequences shown in figures 9-31.

The purified protein typically encodes an insect, vertebrate, fish or mammalian odorant receptor. The mammalian odorant receptor may be a human, rat, mouse or dog.

In one embodiment the invention provides a novel purified protein which belong to a class of proteins which have 7 transmembrane regions and a third cytoplasmic loop from the N-terminus which is approximately 17 amino acid long and to nucleic acid molecules encoding such proteins.

The invention provides methods of transforming cells which comprises transfecting a suitable host cell with a suitable expression vector containing nucleic acid encoding of the odorant receptor. Techniques for carrying out such transformations on cells are well known to those skilled in the art. (41,42) Additionally, the resulting transformed cells are also provided by the invention. These transformed cells may be either olfactory cells or non-olfactory cells. One advantage of using transformed non-olfactory cells is that the desired odorant receptor will be the only odorant receptor expressed on the cell's surface.

In order to obtain cell lines that express a single receptor type, standard procedures may be used to clone individual cDNAs or genes into expression vectors and then transfect the cloned sequences into mammalian cell lines. This approach has been used with sequences encoding some other members of the seven transmembrane domain superfamily

including the 5HT1c serotonin receptor. (43) The cited work illustrates how members of this superfamily transferred into cell lines may generate immortal cell lines that express high levels of the transfected receptor on the cell surface where it will bind ligand and that such abnormally expressed receptor molecules can transduce signals upon binding to ligand.

The invention also provides a method of identifying a desired odorant ligand which comprises contacting transformed non-olfactory cells expressing a known odorant receptor with a series of odorant ligands to determining which ligands bind to the receptors present on the non-olfactory cells.

Additionally, the invention provides a method of identifying a desired odorant receptor comprising contacting a series of transformed non-olfactory cells with a known odorant ligand and determining which odorant receptor binds with the odorant ligand.

The invention provides a method of detecting an odor which comprises: a) identifying a odorant receptor which binds the desired odorant ligand and; b) imbedding the receptor in a membrane such that when the odorant ligand binds to the receptor so identified a detectable signal is produced. In one embodiment of the invention the membrane used in this method is cellular, including a membrane of an olfactory cell or a synthetic membrane.

The ligand tested for may be the vapors emanating from Cocaine, Marijuana, Heroin, Hashish, Angel Dust, gasoline, decayed human flesh, alcohol, gun powder explosives, plastic explosives or firearms. In another embodiment the ligand tested for may be natural gas, a pheromone, toxic fumes,

noxious fumes or dangerous fumes.

In one embodiment of the invention the detectable signal is a lightbulb lighting up, a buzzer buzzing, a bell ringing, a color change, phosphorescence, or radioactivity.

The invention further provides a method of quantifying the amount of an odorant ligand present in a sample which comprises utilizing the above-mentioned method for odor detection and then quantifying the amount of signal produced.

The invention further provides a method of developing fragrances which comprises identifying a desired odorant receptor by the above method, then contacting non-olfactory cells, which have been transfected with an expression vector containing nucleic acid encoding the desired odorant receptor such that the receptor is expressed upon the surface of the non-olfactory cell, with a series of compounds to determine which compound or compounds bind the receptor.

The invention provides to a method of identifying an "odorant fingerprint" which comprises contacting a series of cells, which have been transformed such that each express a known odorant receptor, with a desired sample and determining the type and quantity of the odorant ligands present in the sample.

The invention provides a method of identifying odorant ligands which inhibit the activity of a desired odorant receptor which comprises contacting the desired odorant receptor with a series of compounds and determining which compounds inhibit the odorant ligand - odorant receptor interaction.

The invention also provides for a method of identifying appetite suppressant compounds which comprises identifying odorant ligands by the method mentioned in the preceding paragraph wherein the desired odorant receptor is that which is associated with the perception of food. Additionally, the invention provides a method of controlling appetite in a subject which comprises contacting the olfactory epithelium of the subject with these odorant ligands. Further the invention provides a nasal spray, to control appetite comprising the compounds identified by the above method in a suitable carrier.

The invention provides a method of trapping odors which comprises contacting a membrane which contains multiples of the desired odorant receptor, with a sample such that the desired odorant ligand is absorbed by the binding of the odorant ligand to the odorant receptor. The invention also provides an odor trap employing this method.

The invention also provides a method of controlling pest populations which comprises identifying odorant ligands by the method mentioned above which are alarm odorant ligands and spraying the desired area with the identified odorant ligands. Additionally, provided by the invention is a method of controlling a pest population which comprises identifying odorant ligands by the above mentioned method, which interfere with the interaction between the odorant ligands and the odorant receptors which are associated with fertility. In one embodiment the pest population is a population of insects or rodents, including mice and rats.

The invention also provides a method of promoting fertility which comprises identifying odorant ligands which interact with the odorant receptors associated with fertility by the above mentioned meth d. Further, the invention provides a

method of inhibiting fertility which comprises employing the above mentioned method to identifying odorant ligands which inhibit the interaction between the odorant ligands and the odorant receptors associated with fertility.

This invention is illustrated in the Experimental Detail section which follow. These sections are set forth to aid in an understanding of the invention but are not intended to, and should not be construed to, limit in any way the invention as set forth in the claims which follow thereafter.

EXPERIMENTAL DETAILS

MATERIALS AND METHODS

Polymerase Chain Reaction

RNA was prepared from the olfactory epithelia of Sprague Dawley rats according to Chirgwin et al. (40) or using RNAzol B (Cinna/Biotecx) and then treated with DNase I (0.1 unit/μg RNA) (Promega). In order to obtain cDNA, this RNA was incubated at 0.1 μg/μl with 5 μM random hexamers (Pharmacia) 1 mM each of dATP, dCTP, dGTP, TTP, and 2 units/μl RNase inhibitor (Promega) in 10 mM TrisCl (pH 8.3), 50 mM KCl, 2.5 mM $MgCl_2$, and 0.001% gelatin for 10 min. at 22°C, and then for a further 45 min. at 37°C following the addition of 20 u./μl of Moloney murine leukemia virus reverse transcriptase (BRL). After heating at 95°C for 3 min., cDNA prepared from 0.2 μg of RNA was used in each of a series of polymerase chain reactions (PCR) containing 10 mM TrisCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, 200 μM each of dATP, dCTP, dGTP, and TTP, 2.5 u. Taq polymerase (Perkin Elmer Cetus), and 2 μM of each PCR

primer. PCR reactions were performed according to the following schedule: 96°C for 45 sec., 55°C for 4 min. (or 45°C for 2 min.), 72°C for 3 min. with 6 sec. extension per cycle for 48 cycles. The primers used for PCR were a series of degenerate oligonucleotides made according to the amino acid sequences found in transmembrane domain 2 and 7 of a variety of different members of the 7 transmembrane domain protein superfamily (19). The regions used correspond to amino acids number 60-70 and 286-295 of clone I15 (Figure 4). Each of five different 5' primers were used in PCR reactions with each of six different 3' primers. The 5' primers had the sequences:

```
      C AC   A  C    CT
A1, AATTGGATICTIGTIAATCTIGCIGTIGCIGCIGA;

      C  C  CA  A    C      C
A2, AATTATTTTCTIGTIAATCTIGCITTIGCIGA;

      CCA   CC     A         C
A3, AATTTITTTATIATITCICTIGCITGIGCIGA;

    A     T       C  T   ACT  C
A4, CGITTICTIATGTGTAACCTITGCTTTGCIGA;

            C        CT  TG
A5, ACIGTITATATIACICATCTIACIATIGCIGA.
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The 3' primers were:

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        TTA       T  CAG   C  C   A
B1, CTGICGGTTCATIAAIACATAIATIATIGGGTT;

    TG GA      G  G  A           A
B2, GATCGTTIAGACAACAATAIATIATIGGGTT;

         A  G        G           A
B3, TCIATGTTAAAIGTIGTATAIATIATIGGGTT;

      T     G        G     A     A
B4, GCCTTIGTAAAIATIGCATAIAGGAAIGGGTT;

      G     AGA    G G     G     A
B5, AAATCIGGGCTICGICAATAIATCAIIGGGTT;

    CT CT      G  G  G     G     A
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B6, GAIGAICCIACAAAAAAATAIATAAAIGGGTT.

An aliquot of each PCR reaction was analyzed by agarose gel electrophoresis and bands of interest were amplified further by performing PCR reactions on pipet tip (approx. 1 μl) plugs of the agarose gels containing those DNAs. Aliquots of these semi-purified PCR products were digested with the restriction enzymes Hae III or Hinf I and the digestion products were compared with the undigested DNAs on agarose gels.

Isolation and Analysis of cDNA Clones

CDNA libraries were prepared according to standard procedures (41, 42) in the cloning vector, λZAP II (Stratagene) using poly A^+ RNA prepared from Sprague Dawley rat epithelia (see above) or from an enriched population of olfactory neurons which had been obtained by a 'panning' procedure, using an antibody against the H blood group antigen (Chembiomed) found on a large percentage of rat olfactory neurons. In initial library screens, 8.5 X 10^5 independent clones from the olfactory neuron library and 1.8 X 10^6 clones from the olfactory epithelium library were screened (41) with a ^{32}P-labeled probe (prime-it, Stratagene) consisting of a pool of gel-isolated PCR products obtained using primers A4 and B6 (see above) in PCR reactions using as template, olfactory epithelium cDNA, rat liver DNA, or DNA prepared from the two cDNA libraries. In later library screens, a mixture of PCR products obtained from 20 cDNA clones with the A4 and B6 primers was used as probe ('P1' probe). In initial screens, phage clones were analyzed by PCR using primers A4 and B6 and those which showed the appropriate size species were purified. In later screens, all position clones were purified, but only those that could be amplified with the B6 primer and a primer

specific for vector sequence were analyzed further. To obtain plasmids from the isolated phage clones, phagemid rescue was performed according to the instructions of the manufacturer of λZAP II (Stratagene). DNA sequence analysis was performed on plasmid DNAs using the Sequenase system (USB), initially with the A4 and B6 primers and later with oligonucleotide primers made according to sequences already obtained.

Northern and Southern Blot Analyses

For Northern blots, poly A^+ RNAs from various tissues were prepared as described above or purchased from Clontech. One μg of each RNA was size fractionated on formaldehyde agarose gels and blotted onto nylon membranes (41, 42). For Southern blots, genomic DNA prepared from Sprague Dawley rat liver was digested with the restriction enzymes Eco RI or Hind III, size fractionated on agarose gels and blotted onto nylon membranes (41, 42). The membranes were dried at 80°C, and then prehybridized in 0.5 M sodium phosphate buffer (pH 7.3) containing 1% bovine serum albumin and 4% sodium dodecyl sulfate. Hybridization was carried out in the same buffer at 65°-70°C for 14-20 hrs. with DNAs labeled with ^{32}P. For the first Northern blot shown, the 'P1' probe (see above under cDNA clone isolation) was used. For the second Northern blot shown, a mix of PCR fragments from seven divergent cDNA clones was used. For Southern blots, the region indicated in clone I15 by amino acids 118 through 251 was amplified from a series of divergent cDNA clones using PCR. The primers used for these reactions had the sequences:

P1, ATGGCITATGATCGITATGTIGC, and

P4, AAIAGIGAIACIATIGAIAGATGIGAICC

These DNAs (or a DNA encompassing transmembrane domains 2 through 7 for clone F6) were labeled and tested for crosshybridization at 70°C. Those DNAs which did not show appreciable crosshybridization were hybridized individually, or as a pool to Southern blots at 70°C.

Rat Sequences used to obtain similar sequences expressed in Humans

There are genes similar to the rat genes discussed above present in humans, these genes may be readily isolated by screening human gene libraries with the cloned rate sequences or by performing PCR experiments on human genomic DNA with primers homologous to the rat sequences. First, PCR experiments were performed with genomic DNA from rat, human, mouse, and several other species. When primers homologous to transmembrane domains 2 and 6 (the A4/B6 primer set used to isolate the original rat sequences) were used, DNA of the appropriate size was amplified from rat, human and mouse DNAs. When these primary PCR reactions were subsequently diluted and subjected to PCR using primers to internal sequences (P1 and P4 primers), smaller DNA species were amplified whose size was that seen when the same primers were used in PCR reactions with the cloned rat cDNAs. Similarly, when the secondary PCR was performed with one outer primer together with one inner primer (ie. A4/P4 or P1/B6), amplified DNAs were obtained whose sizes were also consistent with the amplification of genes similar in sequence and organization to the cloned rat cDNAs. Second, a mix of segments from 20 of the rat cDNAs ('P1" probe) was used to screen libraries constructed from human genomic DNAs. Hybridization under high or low stringency conditions reveals the presence of a large number of cloned human DNA segments that are homologous to the rat sequences. Finally, RNA from a human olfactory tumor (neuroesthesi ma,

NCI-H-1011) cell line has been examined for sequences homologous to those cloned in the rat. cDNA prepared from this RNA was subjected to PCR with the A4/B6 primer set and a DNA species of the appropriate size was seen. This DNA was subcloned and partially sequenced and clearly encodes a member of the olfactory protein family identified in the rat.

The inserted sequence in human clones H3/H5 was amplified by PCR with the A4/B6 primers, gel purified, and then labeled with 32P. The labeled DNA was then hybridized to restriction enzyme human placenta. Multiple hybridizing species were observed with each DNA (See Figure 32). This observation is consistent with the presence of a family of odorant receptor genes in the human genome.

The sequence of clone H5 is hereby shown in Figure 19. In addition, the translated protein sequence is shown in Figure 19.

In other to identify odorant receptors in other species, degenerated primer oligonucleotides homologous to conserved regions within the rat odorant receptor family may be used in PCR reactions with genomic DNA or with cDNA prepared from olfactory tissue RNA from those species.

RESULTS

Cloning the Gene Family

A series of degenerate oligonucleotides were designated which could anneal to conserved regions of members of the superfamily of G-protein coupled seven transmembrane domain receptor genes. Five degenerate oliogonucleotides (A1-5; see Experimental Procedures) matching sequences within transmembrane domain 2, and six degenerate oligonucleotides

(B1-6) matching transmembrane domain 7 were used in all combinations in PCR reactions to amplify homologous sequences in cDNA prepared from rat olfactory epithelium RNA. The amplification products of each PCR reaction were then analyzed by agarose gel electrophoresis. Multiple bands were observed with each of the primer combinations. The PCR products within the size range expected for this family of receptors (600 to 1300 bp) were subsequently picked and amplified further with the appropriate primer pair in order to isolate individual PCR bands. Sixty-four PCR bands isolated in this fashion revealed only one or a small number of bands upon agarose gel electrophoresis. Representatives of these isolated PCR products are shown in Figure 2A.

The isolated PCR products were digested with the endonuclease, Hae III or Hinf I, which recognize four base restriction sites and cut DNA at frequent intervals. In most instances, digestion of the PCR product with Hinf I generated a set of fragments whose molecular weights sum to the size of the original DNA (Figure 2B). These PCR bands are therefore likely to each contain a single DNA species. In some cases, however, restriction digestion yielded a series of fragments whose molecular weights sum to a value greater than that of the original PCR product. The most dramatic example is shown in Figure 2 where the 710 bp, PCR 13 DNA, is cleaved by Hinf I to yield a very large number of restriction fragments whose sizes sum to a value five- to ten-fold greater than that of the original PCR product. These observations indicated that PCR product 13 consists of a number of different species of DNA, each of which could be amplified with the same pair of primer oligonucleotides. In addition, when PCR experiments similar to those described were performed using cDNA library DNAs as templates, a 710 bp PCR product was obtained with the PCR13 primer pair

(A4/B6) with DNA from olfactory cDNA libraries, but not a glioma cDNA library. Moreover, digestion of one of this 710 bp product also revealed the presence of multiple DNA species. In other cases (see PCR product 20, for example), digestion yielded a series of restriction fragments whose molecular weights also sum to a size greater than the starting material. Further analysis, however, revealed that the original PCR product consisted of multiple bands of similar but different sizes.

In order to determine whether the multiple DNA species present in PCR 13 encode members of a family of seven transmembrane domain proteins, PCR 13 DNA was cloned into the plasmid vector Bluescript and five individual clones were subjected to DNA sequence analysis. Each of the five clones exhibited a different DNA sequence, but each encoded a protein which displayed conserved features of the superfamily of seven transmembrane domain receptor proteins. In addition, the proteins encoded by all five clones shared distinctive sequence motifs not found in other superfamily members indicating they were all members of a new family of receptors.

To obtain full-length cDNA clones, cDNA libraries prepared from olfactory epithelium RNA or from RNA of an enriched population of olfactory sensory neurons were screened. The probe used in these initial screens was a mixture of PCR 13 DNA as well as DNA obtained by amplication of rat genomic DNA or DNA from two olfactory cDNA libraries with the same primers used to generate PCR 13 (A4 and B6 primers). Hybridizing plaques were subjected to PCR amplification with the A4/B6 primer set and only those giving a PCR product of the appropriate size (approximately 710 bp) were purified. The frequency of such positive clones in the enriched olfactory neuron cDNA library was approximately five times

greater than the frequency in the olfactory epithelium cDNA library. The increased frequency of positive clones observed in the olfactory neuron library is comparable to the enrichment in olfactory neurons generally obtained in the purification procedure.

The original pair of primers used to amplify PCR 13 DNA were then used to amplify coding segments of 20 different cDNA clones. A mix of these PCR products were labeled and used as probe for further cDNA library screens. This mixed probe was also used in a Northern blot (Figure 3) to determine whether the expression of the gene family is restricted to the olfactory epithelium. The mixed probe detects two diffuse bands centered at 2 and 5 kb in RNA from olfactory epithelium; no hybridization can be detected in brain or spleen. (Later experiments which examined a larger number of tissue RNAs with a more restricted probe will be shown below.) Taken together, these data indicate the discovery of a novel multigene family encoding seven transmembrane domain proteins which are expressed in olfactory epithelium, and could be expressed predominantly or exclusively in olfactory neurons.

<u>The Protein Sequences of Numerous, Olfactory-specific Members of the Seven Transmembrane Domain Superfamily</u>

Numerous clones were obtained upon screening cDNA libraries constructed from olfactory epithelium and olfactory neuron RNA at high stringency. Partial DNA sequences were obtained from 36 clones; 18 of these cDNA clones are different, but all of them encode proteins which exhibit shared sequence motifs indicating that they are members of the family identified in PCR 13 DNA. A complete nucleotide sequence was determined for coding regions of ten of the most divergent clones (Figure 4). The deduced protein sequences

of these cDNAs defines a new multigene family which shares sequence and structural properties with the superfamily of neurotransmitter and hormone receptors that traverse the membrane seven times. This novel family, however, exhibits features different from any other member of the receptor superfamily thus far identified.

Each of the ten sequences contains seven hydrophobic stretches (19-26 amino acids) that represent potential transmembrane domains. These domains constitute the regions of maximal sequence similarity to other members of the seven transmembrane domain superfamily (see legend to Figure 4). On the basis of structural homologies with rhodopsin and the ß-adrenergic receptors, (19) it is likely that the amino termini of the olfactory proteins are located on the extracellular side of the plasma membrane and the carboxyl termini are located in the cytoplasm. In this scheme, three extracellular loops alternate with three intracellular loops to link the seven transmembrane domains (see Figure 5). Analysis of the sequences in figure 4 demonstrates that the olfactory proteins, like other members of the receptor superfamily, display no evidence of an N-terminal signal sequence. As in several other superfamily members, a potential N-linked glycosylation site is present in all ten proteins within the short N-terminal extracellular segment. Other structural features conserved with previously identified members of the superfamily included cysteine residues at fixed positions within the first and second extracellular loops that are thought to form a disulfide bond. Finally, many of the olfactory proteins reveal a conserved cysteine within the C-terminal domain which may serve as a palmitoylation site anchoring this domain to the membrane (21). These features, taken together with several short, conserved sequence motifs (see legend to Figure 4), clearly define this new family as a member of the

superfamily of genes encoding the seven transmembrane domain receptors.

There are, however, important differences between the olfactory protein family and the other seven transmembrane domain proteins described previously and these differences may be relevant to proposed function of these proteins in odor recognition. Structure-function experiments involving in vitro mutagenesis suggest that adrenergic ligands interact with this class of receptor molecule by binding within the plane of the membrane (22, 20). Not surprisingly, small receptor families that bind the same class of ligands, such as the adrenergic and muscarinic acetylcholine receptor families exhibit maximum sequence conservation (often over 80%) within the transmembrane domains. In contrast, the family of receptors discussed in this application shows striking divergence within the third, fourth, and fifth transmembrane domains (Figure 4). The variability in the three central transmembrane domains is highlighted schematically in Figure 5. The divergence in potential ligand binding domains is consistent with the idea that the family of molecules cloned is capable of associating with a large number of odorant of diverse molecular structure.

Receptors which belong to the superfamily of seven transmembrane domain proteins interact with G-proteins to generate intracellular signals. In vitro mutagenesis experiments indicate that one site of association between receptor and G-protein resides within the third cytoplasmic loop (22, 23). The sequence of this cytoplasmic loop in 18 different clones we have characterized is shown in Figure 6A. This loop which is often quite long and of variable length in the receptor superfamily is relatively short (only 17 amino acids) and of fixed length in the 18 clones

examined. Eleven of the 18 different clones exhibit the sequence motif K/R I V S S I (or a close relative) at the N-terminus of this loop. Two of the cDNA clones reveal a different H I T C/W A V motif at this site. If this short loop is a site of contact with G-proteins, it is possible that the conserved motifs may reflect sites of interaction with different G-proteins that activate different intracellular signalling systems in response to odors. In addition, the receptors cloned reveal several serine or threonine residues within the third cytoplasmic loop. By analogy with other G-protein coupled receptors, these residues may represent sites of phosphorylation for specific receptor kinases involved in desensitization. (24)

Subfamilies within the Multigene Family

Figure 6A displays the sequences of the fifth transmembrane domain and the adjacent cytoplasmic loop encoded by L8 of the cDNA clones we have analyzed. As a group, the 18 sequences exhibit considerable divergence within this region. The multigene family, however, can be divided into subfamilies such that the members of a given subfamily share significant sequence conservation. In subfamily B, clones F12 and F13, for example, differ from one another at only four of 44 positions (91% identify), and clearly define a subfamily. Clones F5 and I11 (subfamily D) differ from F12 and F13 at 34-36 positions within this region and clearly define a separate subfamily. Thus, this olfactory-specific multigene family consists of highly divergent subfamilies. If these genes encode odor receptors, it is possible that members of the divergent subfamilies bind odorant of widely differing structural classes. Members of the individual subfamilies could therefore recognize more subtle differences between molecules which belong to the same structural class of molecules structures.

The Size of the Multigene Family

Genomic Southern blotting experiments were preformed and genomic libraries were screened to obtain an estimate of the sizes of the multigene family and the member subfamilies encoding the putative odor receptors. DNAs extending from the 3' end of transmembrane domain 3 to the middle of transmembrane domain 6 were synthesized by PCR from DNA of seven of the divergent cDNA clones (Figure 4). In initial experiments, these DNAs were labeled and hybridized to each other to define conditions under which minimal crosshybridization would be observed among the individual clones. At 70°C, the seven DNAs showed no crosshybridization, or crosshybridized only very slightly. The trace levels of crosshybridization observed are not likely to be apparent upon genomic Southern blot analysis where the amounts of DNA are far lower than in the test cross.

Probes derived from these seven DNAs were annealed under stringent conditions, either individually or as a group, to Southern blots of rat liver DNA digested with the restriction endonucleases Eco RI or Hind III (Figure 7). Examination of the Southern blots reveals that all but one of the cDNAs detects a relatively large, distinctive array of bands in genomic DNA. Clone I15 (probe 7), for example, detects about 17 bands with each restriction endonuclease, whereas clone F9 (probe 1) detects only about 5-7 bands with each enzyme. A single band is obtained with clone I7 (probe 5). PCR experiments using nested primers (TM2/TM7 primers followed by primers to internal sequences) and genomic DNA as template indicate that the coding regions of the members of this multigene family, like those of many members of the G-protein coupled superfamily, may not be interrupted by introns. This observation, together with the fact that most

of the probes only encompasses 400 nucleotides suggests that each band observed in these experiments is likely to represent a different gene. These data suggest that the individual probes chosen are representatives of subfamilies which range in size from a single member to as many as 17 members. A total of about 70 individual bands were detected in this analysis which could represent the presence of at least 70 different genes. Although the DNA probes used in these blots did not crosshybridize appreciably with each other, it is possible that a given gene might hybridize to more than one probe, resulting in an overestimate of gene number. However, it is probable that the total number of bands only reflects a minimal estimate of gene number since it is unlikely that we have isolated representative cDNAs from all of the potential subfamilies and the hybridizations were performed under conditions of very high stringency.

A more accurate estimate of the size of the olfactory-specific gene family was obtained by screening rat genomic libraries. The mix of the seven divergent probes used in Southern blots, or the mix of 20 different probes used in our initial Northern blots (see Figure 3), were used as hybridization probes under high (65°C) or lowered (55°C) stringency conditions in these experiments. Nested PCR (see above) was used to verify that the clones giving a positive signal under low stringency annealing conditions were indeed members of this gene family. It is estimated from these studies that there are between 100 and 200 positive clones per haploid genome. The estimate of the size of the family obtain from screens of genomic libraries again represents a lower limit. Given the size of the multigene family, one might anticipate that many of these genes are linked such that a given genomic clone may contain multiple genes. Thus the data from Southern blotting and screens of genomic libraries indicate that the multigene family identified

consists of one to several hundred member genes which can be divided into multiple subfamilies.

It should be noted that the cDNA probes isolated may not be representative of the full complement of subfamilies within the larger family of olfactory proteins. The isolation of cDNAs, for example, relies heavily on PCR with primers from transmembrane domains 2 and 7 and biases our clones for homology within these regions. Thus, estimates of gene number as well as subsequent estimates of RNA abundance should be considered as minimal.

Expression of the Members of this Multigene Family

Additional Northern blot analyses were preformed to demonstrate that expression of the members of this gene family is restricted to the olfactory epithelium. (Figure 8) Northern blot analysis with a mixed probe consisting of the seven divergent cDNAs used above reveals two diffuse bands about 5 and 2 kb in length in olfactory epithelium RNA. This pattern is the same as that seen previously with the mix of 20 DNAs. No annealing is observed to RNA from the brain or retina or other, nonneural tissues, including lung, liver, spleen, and kidney.

An estimate of the level of expression of this family can be obtained from screens of cDNA libraries. The frequency of positive clones in cDNA libraries made from olfactory epithelium RNA suggests that the abundance of the RNAs in the epithelium is about one in 20,000. The frequency of positive clones is approximately five-fold higher in a cDNA library prepared from RNA from purified olfactory neurons (in which 75% of the cells are olfactory neurons). The increased frequency of positive clones obtained in the olfactory neuron cDNA library is comparabl to the

enrichment we obtain upon purification of olfactory neurons. These observations suggest that this multigene family is expressed largely, if not solely, in olfactory neurons and may not be expressed in other cell types within the epithelium. If each olfactory neuron contains 10^5 mRNA molecules, from the frequency of positive clones we predict that each neuron contains only 25-30 transcripts derived from this gene family. Since the family of olfactory proteins consists of a minimum of a hundred genes, a given olfactory neuron could maximally express only a proportion of the many different family members. These values thus suggest that olfactory neurons will exhibit significant diversity at the level of expression of these olfactory proteins.

<u>Identification of pheromone receptors in vomeronasal organ</u>

The vomeronasal organ (vomeronasal gland) is an accessory olfactory structure that is located near the nasal cavity. Like the olfactory epithelium of the nasal cavity, the olfactory epithelium of the vomeronasal organ contains olfactory sensory neurons. The vomeronasal organ is believed to play an important role in the sensing of pheromones in numerous species. Pheromones are believed to have profound effects on both physiological and behavioral aspects of reproduction. the identification of pheromone receptors would permit the identification of the pheromones themselves. It would also enable one to identify agonists or antagonists that would either mimic the pheromones or block the pheromone receptors from transducing pheromone signals. Such information would be important to the development of species specific pesticides and, conversely, to animal husbandry. The identification of pheromone receptors in human could ultimately lead to the development of contraceptives or to treatments for infertility in humans. It is likely that the identification of pheromone receptors

in low mammals such as rodents would lead to the identification of similar receptors in human.

In order to identify potential pheromone receptors, we isolate RNA from the vomeronasal organs of female rats and prepared cDNA from this RNA. The cDNA was subjected to PCR with several different pairs of degenerate oligonucleotide primers that match sequences present in the rat odorant receptor family. The PCR products were subcloned and the nucleotide sequences of the subcloned DNAs were determined. Each of the subcloned DNAs encodes a protein that belongs to the odorant receptor family. The sequences of the following vomeronasal subclones are shown: J1, J2, J4, J7, J8, J11, J14, J15, J16, J17, J19, J20. In a few cases (J2, J4), the same sequence was amplified with two different primer pairs and the sequence shown is a composite of the two sequences. It is possible that one or more of these molecules, or closely related molecules, serve as pheromone receptors in the rat.

DISCUSSION

The mammalian olfactory system can recognize and discriminate a large number of odorous molecules. Perception in this system, as in other sensory systems, initially involves the recognition of external stimuli by primary sensory neurons. This sensory information is then transmitted to the brain where it is decoded to permit the discrimination of different odors. Elucidation of the logic underlying olfactory perception is likely to require the identification of the specific odorant receptors, the analysis of the extent of receptor diversity and receptor specificity, as well as an understanding of the pattern of receptor expression in the olfactory epithelium.

The odorant receptors are thought to transduce intracellular signals by interacting with G-proteins which activate second messenger systems (12, 13, 14, 15). These proteins are clearly members of the family of G-protein coupled receptors which traverse the membrane seven times (19). The odorant receptors should be expressed specifically in the tissue in which odorant are recognized. The family of olfactory proteins cloned is expressed in the olfactory epithelium. Hybridizing RNA is not detected in brain or retina, or in a host of nonneural tissues. Moreover, expression of this gene family the epithelium may be restricted to olfactory neurons. The family of odorant receptors must be capable of interacting with extremely diverse molecular structures. The genes cloned are members of any extremely large multigene family which exhibit variability in regions thought to be important in ligand binding. The possibility that each member of this large family of seven transmembrane proteins is capable of interacting with only one or a small number of odorant provides a plausible mechanism to accommodate the diversity of odor perception. The properties of the gene family identified suggests that this family is likely to encode a large number of distinct odorant receptors.

<u>Size of the Multigene Family</u>

The size of the receptor repertoire is likely to reflect the range of detectable odors and the degree of structural specificity exhibited by the individual receptors. It has been estimated that humans can identify over 10,000 structurally-distinct odorous ligands. However, this does not necessarily imply that humans possess an equally large repertoire of odorant receptors. For example, binding studies in lower vertebrates suggest that structurally-related odorant may activate the same receptor molecules.

In fish which smell amino acids, the binding of alanine to isolated cilia can be competed by other small polar residues (threonine and serine), but not by the basic amino acids, lysine or arginine (11). These data suggest that individual receptors are capable of associating with several structurally-related ligands, albeit with different affinities. Stereochemical models of olfactory recognition in mammals (25) (based largely on psychophysical, rather than biophysical data) have suggested existence of several primary odor groups including camphoraceous, musky, peppermint, ethereal, pungent, and putrid. In such a model, each group would contain odorant with common molecular configurations which bind to common receptors and share similar odor qualities.

Screens of genomic libraries with mixed probes consisting of divergent family members detect approximately 100 to 200 positive clones per genome. The present estimate of at least 100 genes provides only a lower limit since it is likely that the probes used do not detect all of the possible subfamilies. Moreover, it is probable that many of these genes are linked such that a given genomic clone may contain multiple genes. It is therefore expected that the actual size of the gene family may be considerably higher and this family of putative odorant receptors could constitute one of the largest gene families in the genome.

The characterization of a large multigene family encoding putative odorant receptors suggests that the olfactory system utilizes a far greater number of receptors than the visual system. Color vision, for example, allows the discrimination of several hundred hues, but is accomplished by only three different photoreceptors (1, 2, 3 and 4). The photoreceptors each have different, but overlapping absorption spectra which cover the entire spectrum of

visible wavelengths. Discrimination of color results from comparative processing of the information from these three classes of photoreceptors in the brain. Whereas three photoreceptors can absorb light across the entire visible spectrum, our data suggest that a small number of odorant receptors cannot recognize and discriminate the full spectrum of distinct molecular structures perceived by the mammalian olfactory system. Rather, olfactory perception probably employs an extremely large number of receptors each capable of recognizing a small number of odorous ligands.

Diversity within the Gene Family and the Specificity of Odor Recognition

The olfactory proteins identified in this application are clearly members of the superfamily of receptors which traverse the membrane seven time. Analysis of the proteins encoded by the 18 distinct cDNAs we have cloned reveals structural features which may render this family particularly well suited for the detection of a diverse array of structurally distinct odorant. Experiments with other members of this class of receptors suggest that the ligand binds to its receptor within the plane of the membrane such that the ligand contacts many, if not all of the transmembrane helices. The family of olfactory proteins can be divided into several different subfamilies which exhibit significant sequence divergence within the transmembrane domains. Nonconservative changes are commonly observed within blocks of residues in transmembrane regions 3, 4, and 5 (Figures 4, 5, 6); these blocks could reflect the sites of direct contact with odorous ligands. Some members, for example, have acidic residues in transmembrane domain 3, which in other families are thought to be essential for binding aminergic ligands (20) while other members maintain hydrophobic residues at these positions.

This divergence within transmembrane domains may reflect the fact that the members of the family of odorant receptors must associate with odorant of widely different molecular structures.

These observations suggest a model in which each of the individual subfamilies encode receptors which bind distinct structural classes of odorant. Within a given subfamily, however, the sequence differences are far less dramatic and are often restricted to a small number of residues. Thus, the members of a subfamily may recognize more subtle variations among odor molecules of a given structural class. At a practical level, individual subfamilies may recognize grossly different structures such that one subfamily may associate, for example, with the aromatic compound, benzene and its derivatives, whereas a second subfamily may recognize odorous, short chain, aliphatic molecules. Subtle variations in the structure of the receptors within, for example, the hypothetical benzene subfamily could facilitate the recognition and discrimination of various substituted derivatives such as toluene, xylene or phenol. It should be noted that such a model, unlike previous stereochemical models, does not necessarily predict that molecules with similar structures will have similar odors. The activation of distinct receptors with similar structures could elicit different odors, since perceived odor will depend upon higher order processing of primary sensory information.

<u>Evolution of the Gene Family and the Generation of Diversity</u>

Preliminary evidence from PCR analyses suggests that members of this family of olfactory proteins are conserved in lower vertebrates as well as invertebrates. This gene family presumably expanded over evolutionary time providing mammals with the ability to recognize an increasing diversity of

odorant. Examination of the sequences of the family members cloned from mammals provides some insight into the evolution of this multigene family. Although the chromosomal loci encoding these genes has yet to be characterized, it is likely that at least some member genes will be tandemly arranged in a large cluster as is observed with other large multigene families. A tandem array of this sort provides a template for recombination events including unequal crossing over and gene conversion, that can lead to expansion and further diversification of the sort apparent among the family members we have cloned (26).

The multigene family encoding the olfactory proteins is large: all of the member genes clearly have a common ancestral origin, but have undergone considerable divergence such that individual genes encode proteins that share from 40-80% amino acid identity. Subfamilies are apparent with groups of genes sharing greater homology among themselves than with members of other subfamilies. Examination of the sequences of even the most divergent subfamilies, however, reveals a pattern in which several blocks of conserved residues are interspersed with variable regions. This segmental homology is conceptually similar to the organization of framework and hypervariable domains within the families of immunoglobulin and T cell receptor variable region sequences (27, 28). This analogy goes beyond structural organization and may extend to the function of these two gene families: each family consists of a large number of genes which have diversified over evolutionary time to accommodate the binding of a highly diverse array of ligands. The evolutionary mechanisms responsible for the diversification and maintenance of these large gene families may also be similar. It has been suggested that gene conversion has played a major role in the evolution f immunoglobulin and T cell receptor variable domains (29, 30

and 31). Analysis of the sequence of the putative olfactory receptors reveals at least one instance where a motif from a variable region of one subfamily is found imbedded in the otherwise divergent sequence of a second subfamily, suggesting that conversion has occurred. Such a mixing of motifs from one subfamily to another over evolutionary time would provide additional combinatorial possibilities leading to the generation of diversity.

It should be noted, however, that the combinatorial joining of gene segments by DNA rearrangement during development, which is characteristic of immunoglobulin loci (27), is not a feature of the putative odor receptor gene family. No evidence for DNA rearrangement to generate the diversity of genes cloned has been observed. The entire coding region has been sequenced along with parts of the 5' and 3' untranslated regions of 10 different cDNA clones. The sequences of the coding regions are all different; no evidence has been obtained for constant regions that would suggest DNA rearrangement of the sort seen in the immune system. The observations indicate that the diversity olfactory proteins are coded by a large number of distinct gene sequences.

Although it is unlikely from the data that DNA rearrangement is responsible for the generation of diversity among the putative odorant receptors, it remains possible that DNA rearrangements may be involved in the regulation of expression of this gene family. If each olfactory neuron expresses only one or a small number of genes, then a transcriptional control mechanism must be operative to choose which of the more than one hundred genes within the family will be expressed in a given neuron. Gene conversion from one of multiple silent loci into a single active locus, as observed for the trypanosome-variable surface

glycoproteins (32), provides one attractive model. The gene conversion event could be stochastic, such that a given neuron could randomly express any one of several hundred receptor genes, or regulated (perhaps by positional information), such that a given neuron could only express one or a small number of predetermined receptor types. Alternatively, it is possible that positional information in the olfactory epithelium controls the expression of the family of olfactory receptors by more classical mechanisms that do not involve DNA rearrangement. What ever mechanisms will regulate the expression of receptor genes within this large, multigene family, these mechanisms must accommodate the requirement that olfactory neurons are regenerated every 30-60 days (8) and therefore the expression of the entire repertoire of receptors must be accomplished many times during the life of an organism.

<u>Receptor Diversity and the Central Processing of Olfactory Information</u>

The results suggest the existence of a large family of distinct odorant receptors. Individual members of this receptor family are likely to be expressed by only a small set of the total number of olfactory neurons. The primary sensory neurons within the olfactory epithelium will therefore exhibit significant diversity at the level of receptor expression. The question then emerges as to whether neurons expressing the same receptors are localized in the olfactory epithelium. Does the olfactory system employ a topographic map to discriminate among the numerous odorant? The spatial organization of distinct classes of olfactory sensory neurons, as defined by receptor expression, can now be determined by using the procedures of *in situ* hybridization and immunohistochemistry with probes specific for the individual receptor subtypes. This

information should help to distinguish between different models that have been proposed to explain the coding of diverse odorant stimuli (33).

In one model, sensory neurons that express a given receptor and respond to a given odorant may be localized within defined positions within the olfactory epithelium. This topographic arrangement would also be reflected in the projection of olfactory sensory axons into discrete regions (glomeruli) within the olfactory bulb. In this scheme, the central coding to permit the discrimination of discrete odorant would depend, in part, on the spatial segregation of different receptor populations. Attempts to discern the topographic localization of specific receptors at the level of the olfactory epithelium has led to conflicting results. In some studies, electrophysiological recordings have revealed differences in olfactory responses to distinct odorant in different regions of the olfactory epithelium (34, 35). However, these experiments have been difficult to interpret since the differences in response across the epithelium are often small and are not observed in all studies (36).

A second model argues that sensory neurons expressing distinct odorant receptors are randomly distributed in the epithelium but that neurons responsive to a given odorant project to restricted regions within the olfactory bulb. In this instance, the discrimination of odors would be a consequence of the position of second order neurons in the olfactory bulb, but would be independent of the site of origin of the afferent signals within the epithelium. Mapping of the topographic projections of olfactory neurons has been performed by extracellular recordings from different regions of the bulb (37, 38) and by 2-deoxyglucose autoradiography to map regional activity after exposure to

different odorant (39). These studies suggest that spatially-localized groups of bulbar neurons preferentially respond to different odorant. The existence of specific odorant receptors, randomly distributed through the olfactory epithelium, which converge on a common target within the olfactory bulb, would raise additional questions about the recognition mechanisms used to guide these distinct axonal subsets to their central targets.

Other sensory systems also spatially segregate afferent input from primary sensory neurons. The spatial segregation of information employed, for example, by the visual and somatosensory systems, is used to define the location of the stimulus within the external environment as well as to indicate the quality of the stimulus. In contrast, olfactory processing does not extract spatial features of the odorant stimulus. Relieved of the necessity to encode information about the spatial localization of the sensory stimulus, it is possible that the olfactory system of mammals uses the spatial segregation of sensory input solely to encode the identity of the stimulus itself. The molecular identification of the genes likely to encode a large family of olfactory receptors should provide initial insights into the underlying logic of olfactory processing in the mammalian nervous system.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Columbia University in the City of N.Y., The Trustees of

(ii) TITLE OF INVENTION: ODORANT RECEPTORS AND USES THEREOF

(iii) NUMBER OF SEQUENCES: 36

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: COOPER & DUNHAM
(B) STREET: 30 Rockefeller Plaza
(C) CITY: New York
(D) STATE: New York
(E) COUNTRY: U.S.A.
(F) ZIP: 10112

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 681,880
(B) FILING DATE: 05-APR-1991

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: White, John P.
(B) REGISTRATION NUMBER: 28,678
(C) REFERENCE/DOCKET NUMBER: 38586

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (212) 977-9550
(B) TELEFAX: (212) 664-0525
(C) TELEX: (212) 422523 COOP UI

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 954 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:

(B) CLONE: F12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1002 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: F3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 942 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: F5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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GACCGATTTG TGGCCATATG CCACCCTTTA CACTACACAA CAAAGATGAC CCGTCAGCTC 420
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ATCACCTGTG CTGTCCTCAG AGTCTCATCC CCCAGGGGAG GATGGAAATC CTTCTCCACC 720
TGTGGCTCCC ACCTGGCTGT GGTCTGCCTC TTCTATGGCA CCGTCATCGC TGTGTATTTC 780
AACCCATCAT CCTCTCACTT AGCTGGGAGG GACATGGCAG CTGCAGTGAT GTATGCAGTG 840
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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 936 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: F6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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CCCATGTACT TCTTCCTCTG CAACCTCTCC TTCCTGGAGA TCTGGTTCAC CACAGCCTGC 240
GTACCCAAGA CCCTGGCCAC ATTTGCGCCT CGGGGTGGAG TCATTTCCTT GGCTGGCTGT 300

GCCACACAGA TGTACTTTGT CTTTTCTTTG GGCTGTACCG AGTACTTCCT GCTGGCTGTG 360

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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 939 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: I14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 945 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: I15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 933 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: I3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

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(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 984 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: I7

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

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(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 939 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: I8

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

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GCAGCAAGAT TGTCTTTTTG TGAGAACAAT GTACTCCTCA ACTTTTTCTG TGACCTGTTT 540

GTTCTCCTAA AGTTGGCCTG CTCAGACACT TATGTTAATG AGTTGATGAT ACATATCATG 600

GGCGTGATCA TCATTGTTAT TCCATTCGTG CTCATTGTTA TATCCTATGC CAAGATCATC 660

TCCTCCATTC TTAAGGTTCC ATCTACTCAA AGCATTCACA AGGTCTTCTC CACTTGTGGT 720

TCTCATCTCT CTGTGGTGTC TCTGTTCTAC GGGACAATTA TTGGTCTCTA TTTATGTCCA 780

TCAGGTGATA ATTTTAGTCT AAAGGGGTCT GCCATGGCTA TGATGTACAC AGTGGTAACT 840

CCAATGCTGA ACCCGTTCAT CTACAGCCTA AGAAACAGAG ACATGAAGCA GGCCCTAATA 900

AGAGTTACCT GTAGCAAGAA AATCTCTCTG CCATGGTAG 939

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 945 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: I9

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
ATGACTAGAA GAAACCAAAC TGCCATCTCT CAGTTCTTCC TTCTGGGCCT GCCATTCCCC    60
CCAGAGTACC AACACCTGTT CTATGCCCTG TTCCTGGCCA TGTACCTCAC CACTCTCCTG   120
GGGAACCTCA TCATCATCAT CCTCATTCTA CTGGACTCCC ATCTCCACAC ACCCATGTAC   180
TTGTTTCTCA GCAATTTATC CTTTGCCGAC CTCTGTTTTT CCTCTGTCAC AATGCCCAAG   240
TTGTTGCAGA ACATGCAGAG CCAAGTTCCA TCCATCCCCT ATGCAGGGTG CCTGGCACAG   300
ATATACTTCT TTCTGTTTTT TGGAGACCTT GGAAACTTCC TGCTTGTGGC CATGGCCTAT   360
GACCGCTATG TGGCCATCTG CTTCCCCCTT CATTACATGA GCATCATGAG CCCCAAGCTC   420
TGTGTGAGTC TGGTGGTGCT GTCCTGGGTG CTGACTACCT TCCATGCCAT GCTGCACACC   480
CTGCTCATGG CCAGATTGTC ATTCTGTGAG GACAGTGTGA TCCCTCACTA TTTCTGTGAT   540
ATGTCTACTC TGCTGAAAGT GGCTTGTTCT GACACCCATG ATAATGAATT AGCAATATTT   600
ATCTTAGGGG GCCCTATAGT TGTACTACCT TTCCTTCTCA TCATTGTTTC TTATGCAAGA   660
ATTGTTTCCT CCATCTTCAA GGTCCCTTCT TCTCAAAGCA TCCATAAAGC CTTCTCCACC   720
TGTGGCTCCC ACCTGTCTGT GGTGTCACTG TTCTATGGGA CAGTCATTGG TCTCTACTTA   780
TGTCCTTCAG CTAATAACTC CACTGTGAAG GAGACTGTCA TGTCTTTGAT GTACACAATG   840
GTGACACCCA TGCTGAACCC CTTCATCTAC AGCCTAAGAA ACAGAGACAT AAAAGATGCA   900
TTAGAAAAAA TAATGTGCAA AAAGCAAATT CCCTCCTTTC TATGA                   945
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 645 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: homosapien

(vii) IMMEDIATE SOURCE:
(B) CLONE: H5

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..645

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
ATC TGT TTT GTG TCT ACC ACT GTC CCA AAG CAG CTG GTG AAC ATC CAG       48
Ile Cys Phe Val Ser Thr Thr Val Pro Lys Gln Leu Val Asn Ile Gln
  1               5                  10                  15

ACA CAG AGC AGA GTC ATC ACC TAT GCA GAC TGC ATC ACC CAG ATG TGC       96
Thr Gln Ser Arg Val Ile Thr Tyr Ala Asp Cys Ile Thr Gln Met Cys
             20                  25                  30

TTT TTT ATA CTC TTT GTA GTG TTG GAC AGC TTA CTC CTG ACT GTG ATG      144
Phe Phe Ile Leu Phe Val Val Leu Asp Ser Leu Leu Leu Thr Val Met
         35                  40                  45

GCC TAT GAC CGG TTT GTG GCC ATC TGT CAC CCC CTG CAC TAC ACA GTC      192
Ala Tyr Asp Arg Phe Val Ala Ile Cys His Pro Leu His Tyr Thr Val
     50                  55                  60

ATT ATG AGC TCC TGG CTC TGT GGA CTG CTG GTT CTG GTG TCC TGG ATC      240
Ile Met Ser Ser Trp Leu Cys Gly Leu Leu Val Leu Val Ser Trp Ile
 65                  70                  75                  80

GTG AGC ATC CTA TAT TCT CTG TTA CAA AGC ATA ATG GCA TTG CAG CTG      288
Val Ser Ile Leu Tyr Ser Leu Leu Gln Ser Ile Met Ala Leu Gln Leu
                 85                  90                  95

TCC TTC TGT ACA GAA CTG AAA ATC CCT CAA TTT TTC TGT GAA CTT AAT      336
Ser Phe Cys Thr Glu Leu Lys Ile Pro Gln Phe Phe Cys Glu Leu Asn
            100                 105                 110

CAG GTC ATC CAC CTT GCC TGT TCC GAC ACT TTT ATT AAT GAC ATG ATG      384
Gln Val Ile His Leu Ala Cys Ser Asp Thr Phe Ile Asn Asp Met Met
        115                 120                 125

ATG AAT TTT ACA AGT GTG CTG CTG GGT GGG GGA TGC CTC GCT GGA ATA      432
Met Asn Phe Thr Ser Val Leu Leu Gly Gly Gly Cys Leu Ala Gly Ile
    130                 135                 140

TTT TAC TNN TAC TTT AAG ATA CTT TGT TGC ATA TGT TCG ATC TCA TCA      480
Phe Tyr Xaa Tyr Phe Lys Ile Leu Cys Cys Ile Cys Ser Ile Ser Ser
145                 150                 155                 160

GCT CAG GGG ATG AAT AAA GCA CTT TCC ACC TGT GCA TCT CAC CTC TCA      528
Ala Gln Gly Met Asn Lys Ala Leu Ser Thr Cys Ala Ser His Leu Ser
                165                 170                 175
```

```
GTT GTC TCC TTA TTT TAT TGT ACA GGC GTA GGT GTG TAC CTT AGT TCT      576
Val Val Ser Leu Phe Tyr Cys Thr Gly Val Gly Val Tyr Leu Ser Ser
            180                 185                 190

GCT GCA ACC CAT AAC TCA CTC TCA AAT GCT GCA GCC TCG GTG ATG TAC      624
Ala Ala Thr His Asn Ser Leu Ser Asn Ala Ala Ala Ser Val Met Tyr
        195                 200                 205

ACT GTG GTC ACC TCC ATG CTG                                          645
Thr Val Val Thr Ser Met Leu
    210                 215
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 215 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Ile Cys Phe Val Ser Thr Thr Val Pro Lys Gln Leu Val Asn Ile Gln
1               5                   10                  15

Thr Gln Ser Arg Val Ile Thr Tyr Ala Asp Cys Ile Thr Gln Met Cys
            20                  25                  30

Phe Phe Ile Leu Phe Val Val Leu Asp Ser Leu Leu Leu Thr Val Met
        35                  40                  45

Ala Tyr Asp Arg Phe Val Ala Ile Cys His Pro Leu His Tyr Thr Val
    50                  55                  60

Ile Met Ser Ser Trp Leu Cys Gly Leu Leu Val Leu Val Ser Trp Ile
65                  70                  75                  80

Val Ser Ile Leu Tyr Ser Leu Leu Gln Ser Ile Met Ala Leu Gln Leu
                85                  90                  95

Ser Phe Cys Thr Glu Leu Lys Ile Pro Gln Phe Phe Cys Glu Leu Asn
            100                 105                 110

Gln Val Ile His Leu Ala Cys Ser Asp Thr Phe Ile Asn Asp Met Met
        115                 120                 125

Met Asn Phe Thr Ser Val Leu Leu Gly Gly Gly Cys Leu Ala Gly Ile
    130                 135                 140

Phe Tyr Xaa Tyr Phe Lys Ile Leu Cys Cys Ile Cys Ser Ile Ser Ser
145                 150                 155                 160

Ala Gln Gly Met Asn Lys Ala Leu Ser Thr Cys Ala Ser His Leu Ser
                165                 170                 175

Val Val Ser Leu Phe Tyr Cys Thr Gly Val Gly Val Tyr Leu Ser Ser
            180                 185                 190

Ala Ala Thr His Asn Ser Leu Ser Asn Ala Ala Ala Ser Val Met Tyr
        195                 200                 205
```

```
Thr Val Val Thr Ser Met Leu
    210                 215
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 640 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J1

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..640

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
C ATC TGC TTT ACT TCT GCT AGC ATC CCA AAG ATG CTA GTG AAT ATA       46
  Ile Cys Phe Thr Ser Ala Ser Ile Pro Lys Met Leu Val Asn Ile
  1               5                   10                  15

CAG ACG AAG AAC AAG GTG ATC ACC TAT GAA GGC TGC ATC TCC CAA GTA     94
Gln Thr Lys Asn Lys Val Ile Thr Tyr Glu Gly Cys Ile Ser Gln Val
                20                  25                  30

TAC TTT TCA TAC TCT TTG GAG TTT TGG ACA ACT TTC TTC TCG ACT GTG    142
Tyr Phe Ser Tyr Ser Leu Glu Phe Trp Thr Thr Phe Phe Ser Thr Val
            35                  40                  45

ATG GCC TAT GAC CGA TAT GTG GCC ATC TGT CAC CCA TCT NAC TAC ACA    190
Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys His Pro Ser Xaa Tyr Thr
        50                  55                  60

GGT CAT CAT GAA CCN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN    238
Gly His His Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    65                  70                  75

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN    286
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
80                  85                  90                  95

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN    334
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                100                 105                 110

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN    382
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
```

```
                115                   120                  125
NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NTT      430
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        130                 135                 140

TAT TCT TAC TCT AAG ATA GTT TCC TCC ATA CGA GAA ATC TCA TCA TCA      478
Tyr Ser Tyr Ser Lys Ile Val Ser Ser Ile Arg Glu Ile Ser Ser Ser
    145                 150                 155

CAG GGA AAG TAC AAG NNA TTC TCC ACC TGT GCA TCC CAC CTC TCA GTT      526
Gln Gly Lys Tyr Lys Xaa Phe Ser Thr Cys Ala Ser His Leu Ser Val
160                 165                 170                 175

GTT TCA TTA TTC TAT TCT ACA CTT TTG GGT GTG TAC CTT AGT TCT TCT      574
Val Ser Leu Phe Tyr Ser Thr Leu Leu Gly Val Tyr Leu Ser Ser Ser
                180                 185                 190

TTT ACC CAA AAC TCA CAC TCA ACT GCA CGG GCA TCT GTT ATG TAC AGT      622
Phe Thr Gln Asn Ser His Ser Thr Ala Arg Ala Ser Val Met Tyr Ser
            195                 200                 205

GTG GTC ACC CCC ATG TTG                                              640
Val Val Thr Pro Met Leu
        210
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 213 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Ile Cys Phe Thr Ser Ala Ser Ile Pro Lys Met Leu Val Asn Ile Gln
1               5                   10                  15

Thr Lys Asn Lys Val Ile Thr Tyr Glu Gly Cys Ile Ser Gln Val Tyr
            20                  25                  30

Phe Ser Tyr Ser Leu Glu Phe Trp Thr Thr Phe Phe Ser Thr Val Met
        35                  40                  45

Ala Tyr Asp Arg Tyr Val Ala Ile Cys His Pro Ser Xaa Tyr Thr Gly
    50                  55                  60

His His Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                85                  90                  95

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            100                 105                 110

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        115                 120                 125
```

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr
130 135 140

S r Tyr Ser Lys Ile Val Ser Ser Il Arg Glu Il S r Ser Ser Gln
145 150 155 160

Gly Lys Tyr Lys Xaa Phe Ser Thr Cys Ala Ser His Leu Ser Val Val
165 170 175

Ser Leu Phe Tyr Ser Thr Leu Leu Gly Val Tyr Leu Ser Ser Ser Phe
180 185 190

Thr Gln Asn Ser His Ser Thr Ala Arg Ala Ser Val Met Tyr Ser Val
195 200 205

Val Thr Pro Met Leu
210

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 636 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J2

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..636

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ACC TCC ACC ACC ATC CCA AAG ATG CTG GTA AAT ATA CAC ACC CAG AGC 48
Thr Ser Thr Thr Ile Pro Lys Met Leu Val Asn Ile His Thr Gln Ser
1 5 10 15

AAT ACT ATC ACC TAT GAA GAC TGT ATT TCC CAG ATG TTT GTA CTC TTG 96
Asn Thr Ile Thr Tyr Glu Asp Cys Ile Ser Gln Met Phe Val Leu Leu
20 25 30

GTT TTT GGA GAA CTG GAC AAC TTT CTC CTG GCT GTG ATG GCC TAT GAT 144
Val Phe Gly Glu Leu Asp Asn Phe Leu Leu Ala Val Met Ala Tyr Asp
35 40 45

CGA TAT GTG GCT ATC TGT CAC CCA CTG TAT TAC ACA GTC ATT GTG AAC 192
Arg Tyr Val Ala Ile Cys His Pro Leu Tyr Tyr Thr Val Ile Val Asn
50 55 60

CAC CGA CTC TGT ATC CTG CTG CTT CTG CTG TCC TGG GTT GTC AGC ATT 240
His Arg Leu Cys Ile Leu Leu Leu Leu L u S r Trp Val Val Ser Il
65 70 75 80

TTA CAT GCC TTC TTA CAG AGC TTA ATT GTA CTA CAG TTG ACC TTC TGT 288
Leu His Ala Phe Leu Gln Ser Leu Ile Val Leu Gln Leu Thr Phe Cys
85 90 95

GGA GAT GTG AAA ATC CCT CAC TTC TTC TGT GAG CTC AAT CAG CTG TCC 336
Gly Asp Val Lys Ile Pro His Phe Phe Cys Glu Leu Asn Gln Leu Ser
100 105 110

CAA CTC ACA TGT TCA GAC AAC TTT CCA AGT CAC CTC ACA ATG CAT CTT 384
Gln Leu Thr Cys Ser Asp Asn Phe Pro Ser His Leu Thr Met His Leu
115 120 125

GTA CCT GTT ATA TTT GCA GCT ATT TCC CTC AGT GGT ATC CTT TAC TCT 432
Val Pro Val Ile Phe Ala Ala Ile Ser Leu Ser Gly Ile Leu Tyr Ser
130 135 140

TAT TTC AAG ATA GTG TCT TCC ATA CGT TCT ATG TCC TCA GTT CAA GGG 480
Tyr Phe Lys Ile Val Ser Ser Ile Arg Ser Met Ser Ser Val Gln Gly
145 150 155 160

AAG TAC AAG GCA TTT TCT ACA TGT GCC TCT CAC CTT TCC ATT GTC TCC 528
Lys Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Ile Val Ser
165 170 175

TTA TTT TAT AGT ACA GGC CTC GGG GTG TAC GTC AGT TCT GCT GTG ATC 576
Leu Phe Tyr Ser Thr Gly Leu Gly Val Tyr Val Ser Ser Ala Val Ile
180 185 190

CGA AGC TCA CAC TCC TCT GCA AGT GCT TCG GTC ATG TAT ACT GTG GTC 624
Arg Ser Ser His Ser Ser Ala Ser Ala Ser Val Met Tyr Thr Val Val
195 200 205

ACC CCC ATG TTG 636
Thr Pro Met Leu
210

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 212 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Thr Ser Thr Thr Ile Pro Lys Met Leu Val Asn Ile His Thr Gln Ser
1 5 10 15

Asn Thr Ile Thr Tyr Glu Asp Cys Ile Ser Gln Met Phe Val Leu Leu
20 25 30

Val Phe Gly Glu Leu Asp Asn Phe Leu Leu Ala Val Met Ala Tyr Asp
35 40 45

Arg Tyr Val Ala Ile Cys His Pro Leu Tyr Tyr Thr Val Ile Val Asn

```
        50                    55                    60
His Arg Leu Cys Ile L u Leu Leu Leu Leu S r Trp Val Val Ser Il
 65                 70                  75                  80

Leu His Ala Phe Leu Gln Ser Leu Ile Val Leu Gln Leu Thr Phe Cys
                 85                  90                  95

Gly Asp Val Lys Ile Pro His Phe Phe Cys Glu Leu Asn Gln Leu Ser
            100                 105                 110

Gln Leu Thr Cys Ser Asp Asn Phe Pro Ser His Leu Thr Met His Leu
        115                 120                 125

Val Pro Val Ile Phe Ala Ala Ile Ser Leu Ser Gly Ile Leu Tyr Ser
    130                 135                 140

Tyr Phe Lys Ile Val Ser Ser Ile Arg Ser Met Ser Ser Val Gln Gly
145                 150                 155                 160

Lys Tyr Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Ile Val Ser
                165                 170                 175

Leu Phe Tyr Ser Thr Gly Leu Gly Val Tyr Val Ser Ser Ala Val Ile
            180                 185                 190

Arg Ser Ser His Ser Ser Ala Ser Ala Ser Val Met Tyr Thr Val Val
        195                 200                 205

Thr Pro Met Leu
    210
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 646 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J4

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..646

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
C ATA GGC TAT TCA TCT TCT GTC ACA CCC AAT ATG CTT GTC AAC TTC      46
```

```
Ile Gly Tyr Ser Ser Ser Val Thr Pro Asn Met Leu Val Asn Phe
 1               5                  10                  15

CTT ATA AAG CAA AAT ACC ATC TCA TAC CTT GGA TGT TCT ATA CAG TTT      94
Leu Ile Lys Gln Asn Thr Ile Ser Tyr Leu Gly Cys Ser Ile Gln Phe
                 20                  25                  30

GGC TCA GCT GCT TTG TTT GGA GGT CTT GAA TGC TTC CTT CTG GCT GCC     142
Gly Ser Ala Ala Leu Phe Gly Gly Leu Glu Cys Phe Leu Leu Ala Ala
            35                  40                  45

ATG GCG TAT GAT CGT TTT GTA GCA ATC TGC AAC CCA CTG CTT TAT TCA     190
Met Ala Tyr Asp Arg Phe Val Ala Ile Cys Asn Pro Leu Leu Tyr Ser
        50                  55                  60

ACG AAA ATG TCC ACA CAA GTC TGT GTC CAG TTG GTT GTG GGA TCT TAT     238
Thr Lys Met Ser Thr Gln Val Cys Val Gln Leu Val Val Gly Ser Tyr
    65                  70                  75

ATA GGG GGA TTT CTT AAT GCC TCC TCT TTT ACC CTT TCC TTT TTT TCC     286
Ile Gly Gly Phe Leu Asn Ala Ser Ser Phe Thr Leu Ser Phe Phe Ser
80                  85                  90                  95

TTG TCC TTC TGT GGA CCA AAT AGA ATC AAT CAC TTT TAC TGT GAT TTT     334
Leu Ser Phe Cys Gly Pro Asn Arg Ile Asn His Phe Tyr Cys Asp Phe
                100                 105                 110

GCT CCG TTA GTA GAA CTT TCT TGC TCT GAT GTC AGT GTT CCT GAT GCT     382
Ala Pro Leu Val Glu Leu Ser Cys Ser Asp Val Ser Val Pro Asp Ala
            115                 120                 125

GTT ACC TCA TTT TCT GCT GCC TCA GTT ACT ATG CTC ACA GTG TTT ATC     430
Val Thr Ser Phe Ser Ala Ala Ser Val Thr Met Leu Thr Val Phe Ile
        130                 135                 140

ATA GCC ATC TCC TAT ACC TAT ATC CTC ATC ACC ATC CTG AAG ATG CGT     478
Ile Ala Ile Ser Tyr Thr Tyr Ile Leu Ile Thr Ile Leu Lys Met Arg
    145                 150                 155

TCC ACT GAG GGT CGA CAG AAA GCA TTC TCT ACC TGC ACT TCC CAC CTC     526
Ser Thr Glu Gly Arg Gln Lys Ala Phe Ser Thr Cys Thr Ser His Leu
160                 165                 170                 175

ACT GCA GTC ACT CTG TGC TAT GGA ACC ATC ACA TTC ATC TAT GTG ATG     574
Thr Ala Val Thr Leu Cys Tyr Gly Thr Ile Thr Phe Ile Tyr Val Met
                180                 185                 190

CCC AAG TCC AGC TAC TCC ACA GAC CAG AAC AAG GTG GTG TCT GTG TTT     622
Pro Lys Ser Ser Tyr Ser Thr Asp Gln Asn Lys Val Val Ser Val Phe
            195                 200                 205

TAT ATG GTG GTG ATC CCC ATG TTG                                     646
Tyr Met Val Val Ile Pro Met Leu
        210                 215
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 215 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: prot in

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Ile Gly Tyr Ser Ser Ser Val Thr Pro Asn Met Leu Val Asn Phe Leu
1 5 10 15

Ile Lys Gln Asn Thr Ile Ser Tyr Leu Gly Cys Ser Ile Gln Phe Gly
20 25 30

Ser Ala Ala Leu Phe Gly Gly Leu Glu Cys Phe Leu Leu Ala Ala Met
35 40 45

Ala Tyr Asp Arg Phe Val Ala Ile Cys Asn Pro Leu Leu Tyr Ser Thr
50 55 60

Lys Met Ser Thr Gln Val Cys Val Gln Leu Val Val Gly Ser Tyr Ile
65 70 75 80

Gly Gly Phe Leu Asn Ala Ser Ser Phe Thr Leu Ser Phe Phe Ser Leu
85 90 95

Ser Phe Cys Gly Pro Asn Arg Ile Asn His Phe Tyr Cys Asp Phe Ala
100 105 110

Pro Leu Val Glu Leu Ser Cys Ser Asp Val Ser Val Pro Asp Ala Val
115 120 125

Thr Ser Phe Ser Ala Ala Ser Val Thr Met Leu Thr Val Phe Ile Ile
130 135 140

Ala Ile Ser Tyr Thr Tyr Ile Leu Ile Thr Ile Leu Lys Met Arg Ser
145 150 155 160

Thr Glu Gly Arg Gln Lys Ala Phe Ser Thr Cys Thr Ser His Leu Thr
165 170 175

Ala Val Thr Leu Cys Tyr Gly Thr Ile Thr Phe Ile Tyr Val Met Pro
180 185 190

Lys Ser Ser Tyr Ser Thr Asp Gln Asn Lys Val Val Ser Val Phe Tyr
195 200 205

Met Val Val Ile Pro Met Leu
210 215

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium

(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: o'factory pithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J7

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..481

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
C ATC TGC AAG CCC CTG CAC TAC ACC ACC ATC ATG AAT AAC CGA GTG      46
  Ile Cys Lys Pro Leu His Tyr Thr Thr Ile Met Asn Asn Arg Val
    1               5                  10                  15

TGC ACA GTT CTA GTC CTC TCC TGT TGG TTT GCT GGC CTG TTG ATC ATC    94
Cys Thr Val Leu Val Leu Ser Cys Trp Phe Ala Gly Leu Leu Ile Ile
                 20                  25                  30

CTC CCA CCT CTT GGT CAT GGC CTC CAG CTG GAG TTC TGT GAC TCC AAT   142
Leu Pro Pro Leu Gly His Gly Leu Gln Leu Glu Phe Cys Asp Ser Asn
             35                  40                  45

GTG ATT GAT CAT TTT GGC TGT GAT GCC TCT CCA ATT CTG CAG ATA ACC   190
Val Ile Asp His Phe Gly Cys Asp Ala Ser Pro Ile Leu Gln Ile Thr
         50                  55                  60

TGC TCA GAC ACG GTA TTT ATA GAG AAA ATT GTC TTG GCT TTT GCC ATA   238
Cys Ser Asp Thr Val Phe Ile Glu Lys Ile Val Leu Ala Phe Ala Ile
     65                  70                  75

CTG ACA CTC ATC ATT ACT CTG GTA TGT GTT GTT CTC TCC TAC ACA TAC   286
Leu Thr Leu Ile Ile Thr Leu Val Cys Val Val Leu Ser Tyr Thr Tyr
 80                  85                  90                  95

ATC ATC AAG ACC ATT TTA AAG TTT CCT TCT GCT CAA CAA AGA AAA AAG   334
Ile Ile Lys Thr Ile Leu Lys Phe Pro Ser Ala Gln Gln Arg Lys Lys
                100                 105                 110

GCC TTT TCT ACA TGT TCT TCC CAC ATG ATT GTG GTT TCC ATC ACC TAT   382
Ala Phe Ser Thr Cys Ser Ser His Met Ile Val Val Ser Ile Thr Tyr
            115                 120                 125

GGG AGC TGT ATT TTC ATC TAC ATC AAA CCT TCA GCG AAG GAA GGG GTA   430
Gly Ser Cys Ile Phe Ile Tyr Ile Lys Pro Ser Ala Lys Glu Gly Val
        130                 135                 140

GCC ATC AAT AAG GTT GTA TCT GTG CTC ACA ACA TCA GTC GCC CCT TTG   478
Ala Ile Asn Lys Val Val Ser Val Leu Thr Thr Ser Val Ala Pro Leu
    145                 150                 155

CTC                                                               481
Leu
160
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Ile Cys Lys Pro Leu His Tyr Thr Thr Ile Met Asn Asn Arg Val Cys
1               5                   10                  15

Thr Val Leu Val Leu Ser Cys Trp Phe Ala Gly Leu Leu Ile Ile Leu
            20                  25                  30

Pro Pro Leu Gly His Gly Leu Gln Leu Glu Phe Cys Asp Ser Asn Val
        35                  40                  45

Ile Asp His Phe Gly Cys Asp Ala Ser Pro Ile Leu Gln Ile Thr Cys
    50                  55                  60

Ser Asp Thr Val Phe Ile Glu Lys Ile Val Leu Ala Phe Ala Ile Leu
65                  70                  75                  80

Thr Leu Ile Ile Thr Leu Val Cys Val Val Leu Ser Tyr Thr Tyr Ile
                85                  90                  95

Ile Lys Thr Ile Leu Lys Phe Pro Ser Ala Gln Gln Arg Lys Lys Ala
            100                 105                 110

Phe Ser Thr Cys Ser Ser His Met Ile Val Val Ser Ile Thr Tyr Gly
        115                 120                 125

Ser Cys Ile Phe Ile Tyr Ile Lys Pro Ser Ala Lys Glu Gly Val Ala
    130                 135                 140

Ile Asn Lys Val Val Ser Val Leu Thr Thr Ser Val Ala Pro Leu Leu
145                 150                 155                 160
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J8

(ix) FEATURE:
(A) NAME/KEY: CDS

(B) LOCATION: 2..481

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
C ATC TGC CAC CCG CTC CAC TAC TCT CTT CTC ATG AGT CCT GAC AAC        46
  Ile Cys His Pro Leu His Tyr Ser Leu Leu Met Ser Pro Asp Asn
  1               5                   10                  15

TGT GCT GCT CTG GTA ACA GTC TCC TGG GTG ACA GGG GTG GGC ACG GGC     94
Cys Ala Ala Leu Val Thr Val Ser Trp Val Thr Gly Val Gly Thr Gly
                20                  25                  30

TTC CTG CCT TCC CTC CTG ATT TCT AAG TTG GAC TTC TGT GGG CCC AAC    142
Phe Leu Pro Ser Leu Leu Ile Ser Lys Leu Asp Phe Cys Gly Pro Asn
            35                  40                  45

CGC ATC AAC CAT TTC TTC TGT GAC CTC CCT CCA TTA ATC CAG CTG TCC    190
Arg Ile Asn His Phe Phe Cys Asp Leu Pro Pro Leu Ile Gln Leu Ser
        50                  55                  60

TGC TCC AGC GTC TTT GTG ACA GAA ATG GCC ATC TTT GTC CTG TCC ATC    238
Cys Ser Ser Val Phe Val Thr Glu Met Ala Ile Phe Val Leu Ser Ile
    65                  70                  75

GCT GTG CTC TGC ATC TGT TTC CTC CTA ACC CNN NNN TCC TAC ATT TTC    286
Ala Val Leu Cys Ile Cys Phe Leu Leu Thr Xaa Xaa Ser Tyr Ile Phe
80                  85                  90                  95

ATA GTG TCC TCC ATT CTG AGA ATC CCT TCC ACT ACC GGC AGG ATG AAG    334
Ile Val Ser Ser Ile Leu Arg Ile Pro Ser Thr Thr Gly Arg Met Lys
                100                 105                 110

ACA TTT TCT ACA TGT GGC TCC CAC CTG GCC GTG GTC ACC ATC TAC TAT    382
Thr Phe Ser Thr Cys Gly Ser His Leu Ala Val Val Thr Ile Tyr Tyr
            115                 120                 125

GGG ACC ATG ATC TCC ATG TAT GTC GGC CCA AAT GCG CAT CTG TCC CCG    430
Gly Thr Met Ile Ser Met Tyr Val Gly Pro Asn Ala His Leu Ser Pro
        130                 135                 140

GAG CTC AAC AAG GTC ATT TCT GTC TTC TAC ACT GTG ATC ACC CCA CTA    478
Glu Leu Asn Lys Val Ile Ser Val Phe Tyr Thr Val Ile Thr Pro Leu
    145                 150                 155

CTG                                                                481
Leu
160
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Ile Cys His Pro Leu His Tyr Ser Leu Leu Met Ser Pro Asp Asn Cys
```

```
 1                   5                   10                  15
Ala Ala Leu Val Thr Val Ser Trp Val Thr Gly Val Gly Thr Gly Phe
            20                  25                  30
Leu Pro Ser Leu Leu Ile Ser Lys Leu Asp Phe Cys Gly Pro Asn Arg
        35                  40                  45
Ile Asn His Phe Phe Cys Asp Leu Pro Pro Leu Ile Gln Leu Ser Cys
    50                  55                  60
Ser Ser Val Phe Val Thr Glu Met Ala Ile Phe Val Leu Ser Ile Ala
65                  70                  75                  80
Val Leu Cys Ile Cys Phe Leu Leu Thr Xaa Xaa Ser Tyr Ile Phe Ile
                85                  90                  95
Val Ser Ser Ile Leu Arg Ile Pro Ser Thr Thr Gly Arg Met Lys Thr
            100                 105                 110
Phe Ser Thr Cys Gly Ser His Leu Ala Val Val Thr Ile Tyr Tyr Gly
        115                 120                 125
Thr Met Ile Ser Met Tyr Val Gly Pro Asn Ala His Leu Ser Pro Glu
    130                 135                 140
Leu Asn Lys Val Ile Ser Val Phe Tyr Thr Val Ile Thr Pro Leu Leu
145                 150                 155                 160
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 646 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J11

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..646

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
N GTC TGC TTC TCC TCC ACC ACT GTC CCC AAG GTA CTG GCT AAC CAC     46
  Val Cys Phe Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His
   1               5                  10                  15
```

```
ATA CTC AGT AGT CAG GCC ATT TCC TTC TCT GGG TGT CTA ACT CAG CTG      94
Ile Leu Ser Ser Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu
                20                  25                  30

TAT TTT CTC TGT GTG TCT GTG AAT ATG GAC AAT TTC CTG CTG GCT GTG     142
Tyr Phe Leu Cys Val Ser Val Asn Met Asp Asn Phe Leu Leu Ala Val
            35                  40                  45

ATG GCC TAT GAC AGA TTT GTG GCC ATA TGC CAC CCT TTG TAC TAC ACA     190
Met Ala Tyr Asp Arg Phe Val Ala Ile Cys His Pro Leu Tyr Tyr Thr
        50                  55                  60

ACA AAG ATG ACC CAC CAG CTC TGT GTC TTG CTG GTG TCT GGA TCA NNN     238
Thr Lys Met Thr His Gln Leu Cys Val Leu Leu Val Ser Gly Ser Xaa
    65                  70                  75

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN     286
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
80                  85                  90                  95

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN     334
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                100                 105                 110

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN     382
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            115                 120                 125

NNN NNN NNN NNN NNN NNN NNT GTG ATC ATG GTC ACC CCA TTT GTC TGC     430
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Val Ile Met Val Thr Pro Phe Val Cys
        130                 135                 140

ATC CTC ATC TCT TAC ATC TAC ATC ACC AAT GCA GTC CTC AGA GTC TCA     478
Ile Leu Ile Ser Tyr Ile Tyr Ile Thr Asn Ala Val Leu Arg Val Ser
    145                 150                 155

TCC TTT AGG GGA GGA TGG AAA GCC TTC TCC ACC TGT GGC TCA CAC CTG     526
Ser Phe Arg Gly Gly Trp Lys Ala Phe Ser Thr Cys Gly Ser His Leu
160                 165                 170                 175

GCT GTG GTC TGC CTC TTC TAT GGC ACC ATC ATT GCT GTG TAT TTC AAT     574
Ala Val Val Cys Leu Phe Tyr Gly Thr Ile Ile Ala Val Tyr Phe Asn
                180                 185                 190

CCT GTA TCT TCC CAT TCA TCT GAG AAG GAC ACT GCA GCA ACT GTG CTA     622
Pro Val Ser Ser His Ser Ser Glu Lys Asp Thr Ala Ala Thr Val Leu
            195                 200                 205

TAC ACA GTG GTG ACT CCC ATG TTG                                     646
Tyr Thr Val Val Thr Pro Met Leu
        210                 215
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 215 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Val Cys Ph Ser Ser Thr Thr Val Pr Lys Val Leu Ala Asn His Ile
1 5 10 15

Leu Ser Ser Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr
20 25 30

Phe Leu Cys Val Ser Val Asn Met Asp Asn Phe Leu Leu Ala Val Met
35 40 45

Ala Tyr Asp Arg Phe Val Ala Ile Cys His Pro Leu Tyr Tyr Thr Thr
50 55 60

Lys Met Thr His Gln Leu Cys Val Leu Leu Val Ser Gly Ser Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Val Ile Met Val Thr Pro Phe Val Cys Ile
130 135 140

Leu Ile Ser Tyr Ile Tyr Ile Thr Asn Ala Val Leu Arg Val Ser Ser
145 150 155 160

Phe Arg Gly Gly Trp Lys Ala Phe Ser Thr Cys Gly Ser His Leu Ala
165 170 175

Val Val Cys Leu Phe Tyr Gly Thr Ile Ile Ala Val Tyr Phe Asn Pro
180 185 190

Val Ser Ser His Ser Ser Glu Lys Asp Thr Ala Ala Thr Val Leu Tyr
195 200 205

Thr Val Val Thr Pro Met Leu
210 215

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 646 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J14

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..646

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
T GTC TGC TTC TCC TCC ACC ACT GTC CCC AAG GTA CTG GCT AAC CAC      46
  Val Cys Phe Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His
  1               5                   10                  15

ATA CTC AGT AGT CAG GCC ATT TCC TTC TCT GGG TGT CTA ACT CAG CTG    94
Ile Leu Ser Ser Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu
                20                  25                  30

TAT TTT CTC TGT GTG TCT GTG AAT ATG GAC AAT TTC CTG CTG GCT GTG   142
Tyr Phe Leu Cys Val Ser Val Asn Met Asp Asn Phe Leu Leu Ala Val
            35                  40                  45

ATG GCC TAT GAC AGA TTT GTG GCC ATA TGC CAC CCT TTG TAC TAC ACA   190
Met Ala Tyr Asp Arg Phe Val Ala Ile Cys His Pro Leu Tyr Tyr Thr
        50                  55                  60

ACA CCG ATG ACC CAC CAG CTC TGT GTC TTG CTG GTG TCT GGA TCA NNN   238
Thr Pro Met Thr His Gln Leu Cys Val Leu Leu Val Ser Gly Ser Xaa
    65                  70                  75

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN   286
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
80                  85                  90                  95

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN   334
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                100                 105                 110

NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN NNN   382
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            115                 120                 125

NNN NNN NNN NNN NNN NNN NNT GTG ATC ATG GTC ACC CCA TTT GTC TGC   430
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Val Ile Met Val Thr Pro Phe Val Cys
        130                 135                 140

ATC CTC ATC TCT TAC ATC TAC ATC ACC AAT GCA GTC CTC AGA GTC TCA   478
Ile Leu Ile Ser Tyr Ile Tyr Ile Thr Asn Ala Val Leu Arg Val Ser
    145                 150                 155

TCC TTT AGG GGA GGA TGG AAA GCC TTC TCC ACC TGT GGC TCA CAC CTG   526
Ser Phe Arg Gly Gly Trp Lys Ala Phe Ser Thr Cys Gly Ser His Leu
160                 165                 170                 175

GCT GTG GTC TGC CTC TTC TAT GGC ACC ATC ATT GCT GTG TAT TTC AAT   574
Ala Val Val Cys Leu Phe Tyr Gly Thr Ile Ile Ala Val Tyr Phe Asn
                180                 185                 190

CCT GTA TCT TCC CAT TCA TCT GAG AAG GAC ACT GCA GCA ACT GTG CTA   622
Pro Val Ser Ser His Ser Ser Glu Lys Asp Thr Ala Ala Thr Val Leu
            195                 200                 205
```

TAC ACA GTG GTG ACT CCC ATG TTG 646
Tyr Thr Val Val Thr Pro Met Leu
        210   215

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 215 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Val Cys Phe Ser Ser Thr Thr Val Pro Lys Val Leu Ala Asn His Ile
  1               5                  10                  15

Leu Ser Ser Gln Ala Ile Ser Phe Ser Gly Cys Leu Thr Gln Leu Tyr
             20                  25                  30

Phe Leu Cys Val Ser Val Asn Met Asp Asn Phe Leu Leu Ala Val Met
         35                  40                  45

Ala Tyr Asp Arg Phe Val Ala Ile Cys His Pro Leu Tyr Tyr Thr Thr
     50                  55                  60

Pro Met Thr His Gln Leu Cys Val Leu Leu Val Ser Gly Ser Xaa Xaa
 65                  70                  75                  80

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                 85                  90                  95

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            100                 105                 110

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        115                 120                 125

Xaa Xaa Xaa Xaa Xaa Xaa Val Ile Met Val Thr Pro Phe Val Cys Ile
    130                 135                 140

Leu Ile Ser Tyr Ile Tyr Ile Thr Asn Ala Val Leu Arg Val Ser Ser
145                 150                 155                 160

Phe Arg Gly Gly Trp Lys Ala Phe Ser Thr Cys Gly Ser His Leu Ala
                165                 170                 175

Val Val Cys Leu Phe Tyr Gly Thr Ile Ile Ala Val Tyr Phe Asn Pro
            180                 185                 190

Val Ser Ser His Ser Ser Glu Lys Asp Thr Ala Ala Thr Val Leu Tyr
        195                 200                 205

Thr Val Val Thr Pro Met Leu
    210                 215
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J15

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..481

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
T ATC TGC AAC CCT CTG CGC TAC CCA GTG CTC ATG AGC GGC CGG GTG      46
  Ile Cys Asn Pro Leu Arg Tyr Pro Val Leu Met Ser Gly Arg Val
  1               5                   10                  15

TGC CTG CTC ATG GTC GTG GCC TCC TGG TTG GGA GGA TCC CTC AAC GCC    94
Cys Leu Leu Met Val Val Ala Ser Trp Leu Gly Gly Ser Leu Asn Ala
                20                  25                  30

TCC ATT CAG ACT TCT CTG ACC CTT CAG TTC CCC TAC TGT GGA TCA CGG   142
Ser Ile Gln Thr Ser Leu Thr Leu Gln Phe Pro Tyr Cys Gly Ser Arg
            35                  40                  45

AAG ATC TCC CAC TTC TTC TGT GAG GTG CCC TCG CTG CTG ANN NTG GCC   190
Lys Ile Ser His Phe Phe Cys Glu Val Pro Ser Leu Leu Xaa Xaa Ala
        50                  55                  60

TGT GCA GAC ACT GAA GCC TAT GAG CAG GTA CTA TTT GTG ACA GGC GTG   238
Cys Ala Asp Thr Glu Ala Tyr Glu Gln Val Leu Phe Val Thr Gly Val
    65                  70                  75

GTG GTC CTC CTG GTG CCC ATT ACA TTC ATT ACT GCC TCT TAT GCC CTC   286
Val Val Leu Leu Val Pro Ile Thr Phe Ile Thr Ala Ser Tyr Ala Leu
80                  85                  90                  95

ATC CTG GCT GCT GTG CTC CGA ATG CAC TCT GCG GAG GGG AGT CAG AAG   334
Ile Leu Ala Ala Val Leu Arg Met His Ser Ala Glu Gly Ser Gln Lys
                100                 105                 110

GCC CTA GCC ACA TGC TCC TCT CAC CTG ACA GTC GTC AAT CTC TTC TAT   382
Ala Leu Ala Thr Cys Ser Ser His Leu Thr Val Val Asn Leu Phe Tyr
            115                 120                 125

GGG CCC CTT GTC TAC ACC TAC ATG TTA CCT GCT TCC TAT CAC TCA CCA   430
Gly Pro Leu Val Tyr Thr Tyr Met Leu Pro Ala Ser Tyr His Ser Pro
        130                 135                 140
```

```
GGC CAA GAC GAC ATA GTA TCC GTC TTT TAC ACC GTT CTC ACA CCC ATG
Gly Gln Asp Asp Il  Val Ser Val Ph  Tyr Thr Val Leu Thr Pro M t      478
    145                 150                 155

CTT
Leu                                                                  481
160
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Ile Cys Asn Pro Leu Arg Tyr Pro Val Leu Met Ser Gly Arg Val Cys
 1               5                  10                  15

Leu Leu Met Val Val Ala Ser Trp Leu Gly Gly Ser Leu Asn Ala Ser
            20                  25                  30

Ile Gln Thr Ser Leu Thr Leu Gln Phe Pro Tyr Cys Gly Ser Arg Lys
        35                  40                  45

Ile Ser His Phe Phe Cys Glu Val Pro Ser Leu Leu Xaa Xaa Ala Cys
    50                  55                  60

Ala Asp Thr Glu Ala Tyr Glu Gln Val Leu Phe Val Thr Gly Val Val
65                  70                  75                  80

Val Leu Leu Val Pro Ile Thr Phe Ile Thr Ala Ser Tyr Ala Leu Ile
                85                  90                  95

Leu Ala Ala Val Leu Arg Met His Ser Ala Glu Gly Ser Gln Lys Ala
            100                 105                 110

Leu Ala Thr Cys Ser Ser His Leu Thr Val Val Asn Leu Phe Tyr Gly
        115                 120                 125

Pro Leu Val Tyr Thr Tyr Met Leu Pro Ala Ser Tyr His Ser Pro Gly
    130                 135                 140

Gln Asp Asp Ile Val Ser Val Phe Tyr Thr Val Leu Thr Pro Met Leu
145                 150                 155                 160
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J16

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..481

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
C ATC TGT AGG CCT CTT CAC TAT CCT ACC CTC ATG ACC CAG ACA CTG      46
  Ile Cys Arg Pro Leu His Tyr Pro Thr Leu Met Thr Gln Thr Leu
   1               5                  10                  15

TGT GCC AAG ATT GCC ACT GGT TGC TGG TTG GGA GGC TTG GCT GGG CCA    94
Cys Ala Lys Ile Ala Thr Gly Cys Trp Leu Gly Gly Leu Ala Gly Pro
                20                  25                  30

GTG GTA GAA ATT TCC TTG GTG TCT CGT CTC CTT TTT TGT GGC CCC AAT   142
Val Val Glu Ile Ser Leu Val Ser Arg Leu Leu Phe Cys Gly Pro Asn
            35                  40                  45

CAC ATT CAA CAC ATC TTT TGT GAT TTC CCA CCT GTG CTG AGC TTG GCT   190
His Ile Gln His Ile Phe Cys Asp Phe Pro Pro Val Leu Ser Leu Ala
        50                  55                  60

TGT ACT GAT ACA TCA GTG AAT GTC CTG GTA GAT TTT ATT ATA AAC CTC   238
Cys Thr Asp Thr Ser Val Asn Val Leu Val Asp Phe Ile Ile Asn Leu
    65                  70                  75

TGC AAG ATC CTG GCC ACC TTC CTG CTG ATC CTG AGC TCC TAC TTG CAG   286
Cys Lys Ile Leu Ala Thr Phe Leu Leu Ile Leu Ser Ser Tyr Leu Gln
80                  85                  90                  95

ATA ATC CGC ACA GTG CTC AAG ATT CCT TCA GCT GCA GGC AAG AAG AAA   334
Ile Ile Arg Thr Val Leu Lys Ile Pro Ser Ala Ala Gly Lys Lys Lys
                100                 105                 110

GCA TTC TCG ACT TGT GCC TCC CAT CTC ACT GTG GTT CTC ATC TTC TAT   382
Ala Phe Ser Thr Cys Ala Ser His Leu Thr Val Val Leu Ile Phe Tyr
            115                 120                 125

GGG AGC ATC CTT TTC ATG TAT GTG CGG CTG AAG AAG ACT TAC TCC CTT   430
Gly Ser Ile Leu Phe Met Tyr Val Arg Leu Lys Lys Thr Tyr Ser Leu
        130                 135                 140

GAC TAC GAC AGA GCC TTG GCA GTA GTC TAC TCC GTG GTT ACC CCT TTC   478
Asp Tyr Asp Arg Ala Leu Ala Val Val Tyr Ser Val Val Thr Pro Phe
    145                 150                 155

CTG                                                               481
Leu
160
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Ile Cys Arg Pro Leu His Tyr Pro Thr Leu Met Thr Gln Thr Leu Cys
1               5                   10                  15

Ala Lys Ile Ala Thr Gly Cys Trp Leu Gly Gly Leu Ala Gly Pro Val
            20                  25                  30

Val Glu Ile Ser Leu Val Ser Arg Leu Leu Phe Cys Gly Pro Asn His
        35                  40                  45

Ile Gln His Ile Phe Cys Asp Phe Pro Pro Val Leu Ser Leu Ala Cys
    50                  55                  60

Thr Asp Thr Ser Val Asn Val Leu Val Asp Phe Ile Ile Asn Leu Cys
65                  70                  75                  80

Lys Ile Leu Ala Thr Phe Leu Leu Ile Leu Ser Ser Tyr Leu Gln Ile
                85                  90                  95

Ile Arg Thr Val Leu Lys Ile Pro Ser Ala Ala Gly Lys Lys Lys Ala
            100                 105                 110

Phe Ser Thr Cys Ala Ser His Leu Thr Val Val Leu Ile Phe Tyr Gly
        115                 120                 125

Ser Ile Leu Phe Met Tyr Val Arg Leu Lys Lys Thr Tyr Ser Leu Asp
    130                 135                 140

Tyr Asp Arg Ala Leu Ala Val Val Tyr Ser Val Val Thr Pro Phe Leu
145                 150                 155                 160
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J17

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..481

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
A ATC TGC AAC CCA CTG CTT TAT TCC ACC AAA ATG TCC ACA CAA GTC        46
  Ile Cys Asn Pro Leu Leu Tyr Ser Thr Lys Met Ser Thr Gln Val
    1               5                  10                  15

TGT ATC CAG TTG GTT GCA GGA TCT TAT ATA GGG GGT TTT CTT AAT ACT      94
Cys Ile Gln Leu Val Ala Gly Ser Tyr Ile Gly Gly Phe Leu Asn Thr
                 20                  25                  30

TGC CTC ATC ATG TTT TAC TTT TTC TCT TTT CTC TTC TGT GGG CCA AAT     142
Cys Leu Ile Met Phe Tyr Phe Phe Ser Phe Leu Phe Cys Gly Pro Asn
             35                  40                  45

ATA GTT GAT CAT TTT TTC TGT GAT TTT GCT CCT TTN NTG GAA CTT TCG     190
Ile Val Asp His Phe Phe Cys Asp Phe Ala Pro Xaa Xaa Glu Leu Ser
         50                  55                  60

TGC TCT GAT GTG AGT GTC TCT GTA GTT GTT ATG TCA TTT TCT GCT GGC     238
Cys Ser Asp Val Ser Val Ser Val Val Val Met Ser Phe Ser Ala Gly
     65                  70                  75

TCA GTT ACT ATG ATC ACA GTG TTT ATC ATA GCC ATC TCC TAT TCT TAC     286
Ser Val Thr Met Ile Thr Val Phe Ile Ile Ala Ile Ser Tyr Ser Tyr
 80                  85                  90                  95

ATC CTC ATC ACC ATC CTG AAG ATG TCC TCA ACT GAG GGC CGT CAC AAG     334
Ile Leu Ile Thr Ile Leu Lys Met Ser Ser Thr Glu Gly Arg His Lys
                100                 105                 110

GCT TTC TCC ACA TGT ACC TCC CAC CTC ACT GCA GTC ACT CTC TAC TAT     382
Ala Phe Ser Thr Cys Thr Ser His Leu Thr Ala Val Thr Leu Tyr Tyr
            115                 120                 125

GGC ACC ATT ACC TTC ATT TAT GTG ATG CCC AAG TCC ACA TAC TCT ACA     430
Gly Thr Ile Thr Phe Ile Tyr Val Met Pro Lys Ser Thr Tyr Ser Thr
        130                 135                 140

GAC CAG AAC AAG GTG GTG TCT GTG TTT TAC ATG GTG GTG ATC CCA ATG     478
Asp Gln Asn Lys Val Val Ser Val Phe Tyr Met Val Val Ile Pro Met
    145                 150                 155

TTG                                                                 481
Leu
160
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Il Cys Asn Pro Leu Leu Tyr Ser Thr Lys Met Ser Thr Gln Val Cys
1   5   10   15

Ile Gln Leu Val Ala Gly Ser Tyr Ile Gly Gly Phe Leu Asn Thr Cys
            20   25   30

Leu Ile Met Phe Tyr Phe Phe Ser Phe Leu Phe Cys Gly Pro Asn Ile
        35   40   45

Val Asp His Phe Phe Cys Asp Phe Ala Pro Xaa Xaa Glu Leu Ser Cys
    50   55   60

Ser Asp Val Ser Val Ser Val Val Val Met Ser Phe Ser Ala Gly Ser
65   70   75   80

Val Thr Met Ile Thr Val Phe Ile Ile Ala Ile Ser Tyr Ser Tyr Ile
                85   90   95

Leu Ile Thr Ile Leu Lys Met Ser Ser Thr Glu Gly Arg His Lys Ala
            100   105   110

Phe Ser Thr Cys Thr Ser His Leu Thr Ala Val Thr Leu Tyr Tyr Gly
        115   120   125

Thr Ile Thr Phe Ile Tyr Val Met Pro Lys Ser Thr Tyr Ser Thr Asp
    130   135   140

Gln Asn Lys Val Val Ser Val Phe Tyr Met Val Val Ile Pro Met Leu
145   150   155   160

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 479 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J19

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..479

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

T ATC TGC CAC CCT CTG AAG TAC ACA GTT ATC ATG AAT CAC TAT TTT 46
Ile Cys His Pro Leu Lys Tyr Thr Val Ile Met Asn His Tyr Phe

```
 1                   5                       10                       15

TGT GTG ATG CTG CTG CTC TTC TCT GTG TTC GTT AGC ATT GCA CAT GCG      94
Cys Val Met Leu Leu Leu Phe Ser Val Phe Val Ser Ile Ala His Ala
                 20                      25                      30

TTG TTC CAC ATT TTA ATG GTG TTG ATA CTG ACT TTC AGC ACA AAA ACT     142
Leu Phe His Ile Leu Met Val Leu Ile Leu Thr Phe Ser Thr Lys Thr
             35                      40                      45

GAA ATC CCT CAC TTT TTC TGT GAG CTG GCT CAT ATC ATC AAA CTT ACC     190
Glu Ile Pro His Phe Phe Cys Glu Leu Ala His Ile Ile Lys Leu Thr
         50                      55                      60

TGT TCC GAT AAT TTT ATC AAC TAT CTG CTG ATA TAC ACA GAG TCT GTC     238
Cys Ser Asp Asn Phe Ile Asn Tyr Leu Leu Ile Tyr Thr Glu Ser Val
     65                      70                      75

TTA TTT TTT GGT GTT CAT ATT GTA GGG ATC ATT TTG TCT TAT ATT TAC     286
Leu Phe Phe Gly Val His Ile Val Gly Ile Ile Leu Ser Tyr Ile Tyr
 80                      85                      90                      95

ACT GTA TCC TCA GTT TTA AGA ATG TCA TTA TTG GGA GGA ATG TAT AAA     334
Thr Val Ser Ser Val Leu Arg Met Ser Leu Leu Gly Gly Met Tyr Lys
                100                     105                     110

GCC TTT TCA ACA TGT GGA TCT CAT TTG TCG GTT GTC TCT GTT TTA TGG     382
Ala Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Ser Val Leu Trp
            115                     120                     125

CAC AGG TTT TGG GGT ACA CAT AAG CTC TCC ACT TAC TGA CTC TCC AAG     430
His Arg Phe Trp Gly Thr His Lys Leu Ser Thr Tyr  *  Leu Ser Lys
        130                     135                     140

GAA GAC TGT AGT GGC TTC AGT GAT GTA CAC TGT GGT TAC TCA GAT GCT G   479
Glu Asp Cys Ser Gly Phe Ser Asp Val His Cys Gly Tyr Ser Asp Ala
    145                     150                     155
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 159 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
Ile Cys His Pro Leu Lys Tyr Thr Val Ile Met Asn His Tyr Phe Cys
 1               5                  10                  15

Val Met Leu Leu Leu Phe Ser Val Phe Val Ser Ile Ala His Ala Leu
            20                  25                  30

Phe His Ile Leu Met Val Leu Ile Leu Thr Phe Ser Thr Lys Thr Glu
        35                  40                  45

Ile Pro His Phe Phe Cys Glu Leu Ala His Ile Ile Lys Leu Thr Cys
    50                  55                  60
```

```
Ser Asp Asn Phe Ile Asn Tyr Leu Leu Ile Tyr Thr Glu Ser Val Leu
 65                 70                  75                  80

Ph  Phe Gly Val His Ile Val Gly Ile Ile Leu Ser Tyr Ile Tyr Thr
                 85                  90                  95

Val Ser Ser Val Leu Arg Met Ser Leu Leu Gly Gly Met Tyr Lys Ala
            100                 105                 110

Phe Ser Thr Cys Gly Ser His Leu Ser Val Val Ser Val Leu Trp His
        115                 120                 125

Arg Phe Trp Gly Thr His Lys Leu Ser Thr Tyr  *  Leu Ser Lys Glu
    130                 135                 140

Asp Cys Ser Gly Phe Ser Asp Val His Cys Gly Tyr Ser Asp Ala
145                 150                 155
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: rat olfactory epithelium
(B) STRAIN: Srpague-Dawley rat
(F) TISSUE TYPE: olfactory epithelium

(vii) IMMEDIATE SOURCE:
(B) CLONE: J20

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..481

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
A ATC TGC TAC CCA CTG AGG TAC CTT CTC ATC ATG AGC TGG GTG GTG        46
  Ile Cys Tyr Pro Leu Arg Tyr Leu Leu Ile Met Ser Trp Val Val
    1               5                  10                  15

TGC ACA GCA CTG TCC GTG GCA ATC TGG GTC ATA GGC TTT TGT GCC TCC      94
Cys Thr Ala Leu Ser Val Ala Ile Trp Val Ile Gly Phe Cys Ala Ser
                 20                  25                  30

GTT ATA CCT CTC TGC TTC ACG ATC CTC CCA CTC TGT GGT CCT TAC GTC     142
Val Ile Pro Leu Cys Phe Thr Ile Leu Pro Leu Cys Gly Pro Tyr Val
             35                  40                  45

GTT GAT TAT CTT TTC TGC GAG CTG CCC ATC CTT CTG CAC CTG TTC TGC     190
Val Asp Tyr Leu Phe Cys Glu Leu Pro Ile Leu Leu His Leu Phe Cys
         50                  55                  60

ACA GAT ACA TCT CTG CTG GAG NNN NNN NNN NNN NNN NNN NNN NNN NNN     238
Thr Asp Thr Ser Leu Leu Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
     65                  70                  75
```

```
NNN NNN NNN NNN NNN CCC TTC CTC CTG ATT GTT CTC TCC TAC CTT CGC     286
Xaa Xaa Xaa Xaa Xaa Pro Phe Leu Leu Ile Val Leu Ser Tyr Leu Arg
 80                  85                  90                  95

ATC CTG GTG GCT GTG ATA AGA ATA GAC TCA GCT GAG GGC AGA AAA AAG     334
Ile Leu Val Ala Val Ile Arg Ile Asp Ser Ala Glu Gly Arg Lys Lys
                100                 105                 110

GCC TTT TCA ACT TGT GCT TCA CAC TTG GCT GTG GTG ACC ATC TAC TAT     382
Ala Phe Ser Thr Cys Ala Ser His Leu Ala Val Val Thr Ile Tyr Tyr
            115                 120                 125

GGA ACA GGG CTG ATC AGG TAC TTG AGG CCC AAG TCC CTT TAT TCC GCT     430
Gly Thr Gly Leu Ile Arg Tyr Leu Arg Pro Lys Ser Leu Tyr Ser Ala
        130                 135                 140

GAG GGA GAC AGA CTG ATC TCT GTG TTC TAT GCA GTC ATT GGC CCT GCA     478
Glu Gly Asp Arg Leu Ile Ser Val Phe Tyr Ala Val Ile Gly Pro Ala
    145                 150                 155

CTG                                                                 481
Leu
160
```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```
Ile Cys Tyr Pro Leu Arg Tyr Leu Leu Ile Met Ser Trp Val Val Cys
  1               5                  10                  15

Thr Ala Leu Ser Val Ala Ile Trp Val Ile Gly Phe Cys Ala Ser Val
             20                  25                  30

Ile Pro Leu Cys Phe Thr Ile Leu Pro Leu Cys Gly Pro Tyr Val Val
         35                  40                  45

Asp Tyr Leu Phe Cys Glu Leu Pro Ile Leu Leu His Leu Phe Cys Thr
     50                  55                  60

Asp Thr Ser Leu Leu Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 65                  70                  75                  80

Xaa Xaa Xaa Xaa Pro Phe Leu Leu Ile Val Leu Ser Tyr Leu Arg Ile
                 85                  90                  95

Leu Val Ala Val Ile Arg Ile Asp Ser Ala Glu Gly Arg Lys Lys Ala
            100                 105                 110

Phe Ser Thr Cys Ala Ser His Leu Ala Val Val Thr Ile Tyr Tyr Gly
        115                 120                 125

Thr Gly Leu Ile Arg Tyr Leu Arg Pro Lys Ser Leu Tyr S r Ala Glu
    130                 135                 140

Gly Asp Arg Leu Ile Ser Val Phe Tyr Ala Val Ile Gly Pr  Ala Leu
145                 150                 155                 160
```

What is claim d is:

1. An isolated nucleic acid molecule encoding an odorant receptor.

2. An isolated DNA of claim 1.

3. An isolated cDNA of claim 2.

4. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 9.

5. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 10.

6. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 11.

7. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 12.

8. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 13.

9. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 14.

10. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 15.

11. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 16.

12. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 17.

13. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 18.

14. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 19.

15. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 20.

16. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 21.

17. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 22.

18. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 23.

19. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 24.

20. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 25.

21. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 26.

22. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 27.

23. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 28.

24. An isolated cDNA of claim 3 wherein the sequence f the cDNA has the nucleotide s quence shown in Figure 29.

25. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 30.

26. An isolated cDNA of claim 3 wherein the sequence of the cDNA has the nucleotide sequence shown in Figure 31.

27. An isolated cDNA of claim 3 encoding an insect odorant receptor.

28. An isolated cDNA of claim 3 encoding a vertebrate odorant receptor.

29. An isolated cDNA of claim 3 encoding a fish odorant receptor.

30. An isolated cDNA of claim 3 encoding a mammalian odorant receptor.

31. An isolated cDNA of claim 30 wherein the mammalian odorant receptor is a human odorant receptor.

32. An isolated cDNA of claim 30 wherein the mammalian odorant receptor is a rat, dog or mouse odorant receptor.

33. An expression vector comprising the cDNA of claim 3 and the sequence elements necessary for replication and expression in a suitable host.

34. An expression vector comprising the cDNA of any of claims 4-19 and the sequence elements necessary for replication and expression in a suitable host.

35. A purified protein encoding an odorant receptor.

36. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 9.

37. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 10.

38. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 11.

39. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 12.

40. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 13.

41. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 14.

42. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 15.

43. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 16.

44. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 17.

45. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 18.

46. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 19.

47. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 20.

48. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 21.

49. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 22.

50. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 23.

51. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 24.

52. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 25.

53. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 26.

54. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 27.

55. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 28.

56. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 29.

57. A purified protein of claim 35 wherein the amino acid sequence is the sequence in Figure 31.

58. A purified protein of claim 35 encoding an insect odorant receptor.

59. A purified protein of claim 35 encoding a vertebrate odorant receptor.

60. A purified protein of claim 35 encoding a fish odorant receptor.

61. A purified protein of claim 35 encoding a mammalian odorant receptor.

62. A purified protein of claim 61 wherein the mammalian odorant receptor is a human odorant receptor.

63. A purified protein of claim 61 wherein the mammalian odorant receptor is a rat, dog or mouse odorant receptor.

64. A purified protein of claim 35 which has 7 transmembrane regions and whose third cytoplasmic loop from the N-terminus is approximately 17 amino acid long.

65. A method of transforming cells which comprises transfecting a host cell with a suitable expression vector of claim 33.

66. A method of transforming cells which comprises transfecting a host cell with a suitable expression vector of claim 34.

67. Cells transformed by the method of claim 65.

68. Transformed cells of claim 67 wherein the cells are olfactory cells.

69. Transformed cells of claim 67 wherein the cells are non-olfactory cells.

70. A method of identifying a desired odorant ligand comprising contacting transformed non-olfactory cells of claim 69, expressing a known odorant receptor with a series of odorant ligands and determining which ligands bind to the receptors present on the non-olfactory cells.

71. A method of identifying a desired odorant receptor comprising contacting a series of transformed non-olfactory cells of claim 69 with a known odorant ligand and determining which odorant receptor binds with the odorant ligand.

72. A method of detecting an odor which comprises:

a) identifying a odorant receptor which binds the desired odorant ligand by the method of claim 71 and;

b) imbedding the receptor in a membrane such that when the odorant ligand binds with the receptor identified in a) above, a detectable signal is produced.

73. A method of claim 72 wherein the desired odorant is a pheromone.

74. A method of claim 72 wherein the desired odorant ligand is the vapors emanating from cocaine, marijuana, heroin, hashish, or angel dust.

75. A method of claim 72 wherein the desired odorant ligand is the vapors emanating from gasoline, natural gas or alcohol.

76. A method of claim 72 wherein the desired odorant ligand is the vapors emanating from decayed human flesh.

77. A method of claim 72 wherein the desired odorant ligand is the vapors emanating from explosives, plastic explosives, firearms, or gun powder.

78. A method of claim 72 wherein the desired odorant ligand is toxic fumes, noxious fumes or dangerous fumes.

79. A method of claim 72 wherein the membrane is a cell membrane.

80. A method of claim 72 wherein the membrane is an olfactory cell membrane.

81. A method of claim 72 wherein the membrane is a synthetic membrane.

82. A method of claim 72 wherein the detectable signal is a color change, phosporescence, or radioactivity.

83. A method of quantifying the amount of an odorant ligand present in a sample which comprises the method of claim 72 wherein the detectable signal is quantified.

84. A method of developing fragrances which comprises identifying a desired odorant receptor by the method of claim 71 then contacting non-olfactory cells, which have been transfected with an expression vector containing the cDNA of the desired odorant receptor such that the receptor is expressed upon the surface of th non-olfactory cell, with a series of compounds to determine which ones bind with the receptor.

85. A method of identifying an odorant fingerprint which comprises contacting a series of cells, which have been transformed such that each express a known odorant receptor, with a desired sample and determining the type and quantity of the odorant ligands present in the sample.

86. A method of identifying odorant ligands which inhibit the activity of a desired odorant receptor which comprises contacting the desired odorant receptor with a series of compounds and determining which compounds inhibit the odorant ligand - odorant receptor interaction.

87. A method of identifying appetite suppressant compounds which comprises identifying odorant ligands by the method of claim 86 wherein the desired odorant receptor is that which is associated with the perception of food.

88. A method of controlling appetite in a subject which comprises contacting the olfactory epithelium of the subject with the odorant ligands identified by the method of claim 87.

89. A nasal spray, to control appetite comprising the compounds identified by the method of claim 87 in a suitable carrier.

90. A method of trapping odors which comprises contacting a membrane which contains multiples of the desired odorant receptor, with a sample such that the desired odorant ligand is absorbed by the binding of the odorant ligand to the odorant receptor.

91. An odor trap employing the method of claim 90.

92. A method of controlling pest populations which comprises identifying odorant ligands by the method of claim 70 which are alarm odorant ligands and spraying the desired area with the identified odorant ligands.

93. A method of controlling a pest population which comprises identifying odorant ligands by the method of claim 70 which interfere with the interaction between the odorant ligands and the odorant receptors which are associated with fertility.

94. A method of claim 92 or 93 wherein the pest population is a population of insects.

95. A method of claim 92 or 93 wherein the pest population is a population of rodents.

96. A method of claim 95 wherein the population of rodents is a population of mice or rats.

97. A method of promoting fertility which comprises employing the method of claim 70 to identify odorant ligands which interact with the odorant receptors associated with fertility and administering the identified odorant ligands to a subject.

98. A method of inhibiting fertility which comprises employing the method of claim 70 to identifying odorant ligands which inhibit the interaction between the odorant ligands and the odorant receptors associated with f rtility and administering the identified odorant ligands to a subject.

Figure 1A

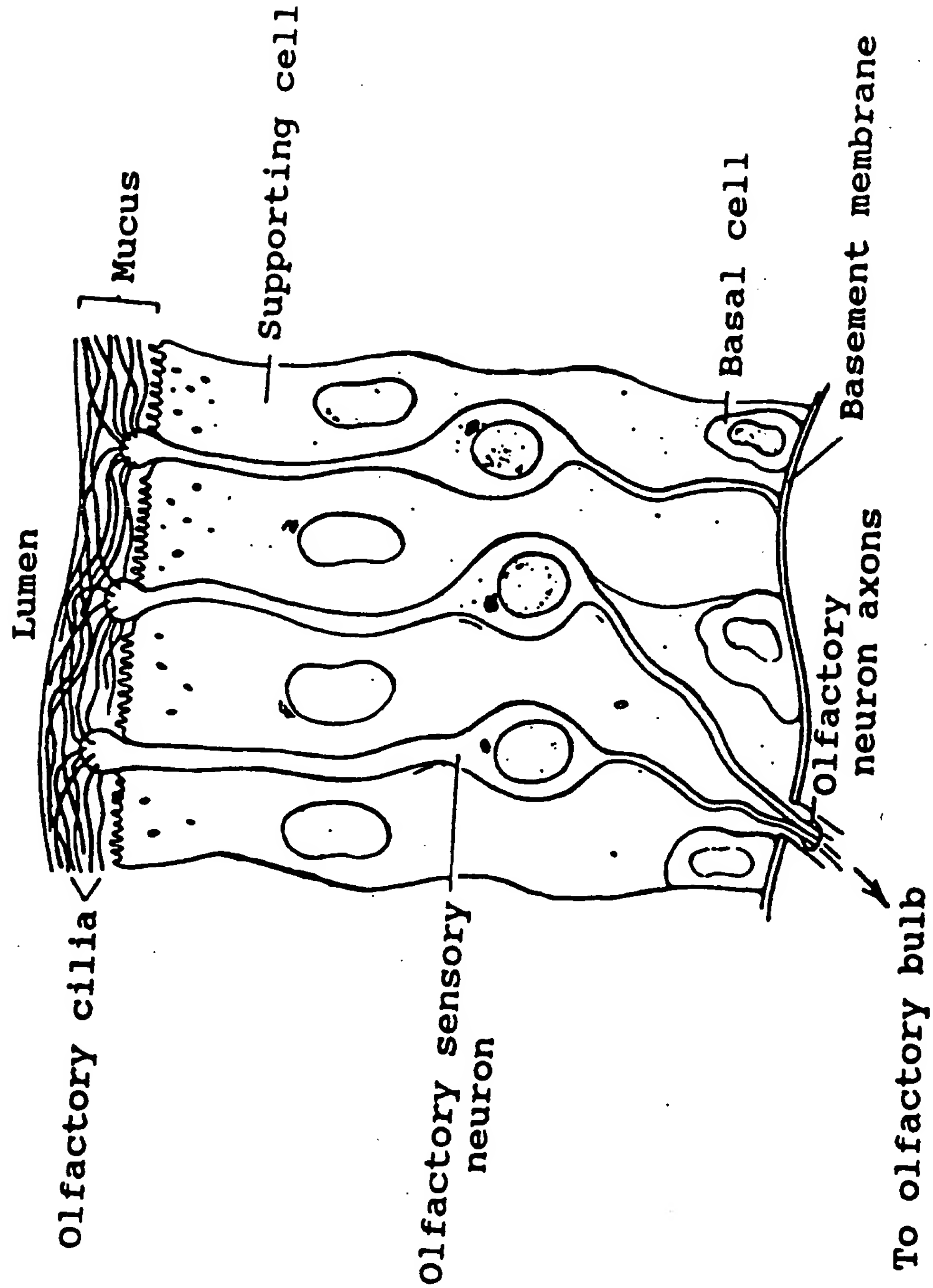
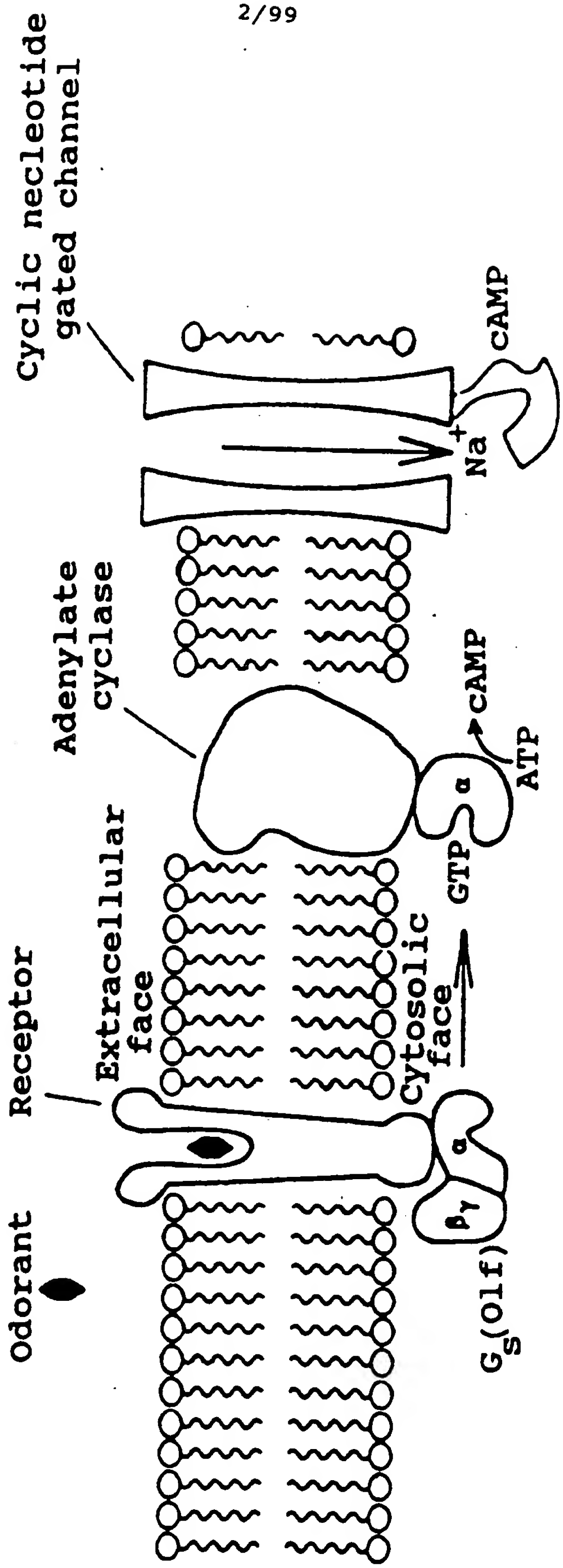

Lumen
Mucus
Supporting cell
Basal cell
Basement membrane
Olfactory neuron axons
Olfactory cilia
Olfactory sensory neuron
To olfactory bulb

Figure 1B


Cyclic necleotide gated channel
cAMP
Na+
Adenylate cyclase
cAMP
ATP
α
GTP
Receptor
Extracellular face
Cytosolic face
Odorant
α
βγ
G_S(Olf)

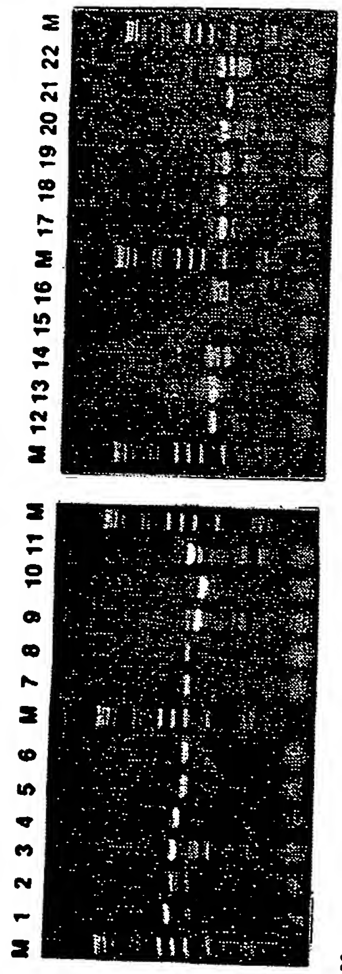


Figure 2A

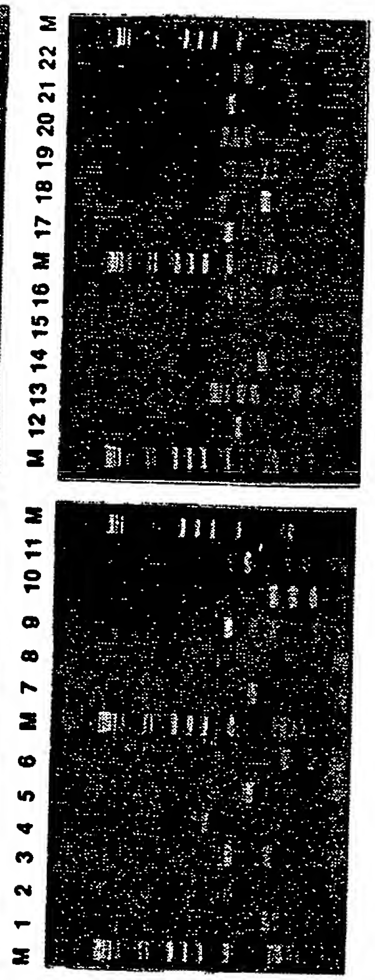


Figure 2B

Figure 3

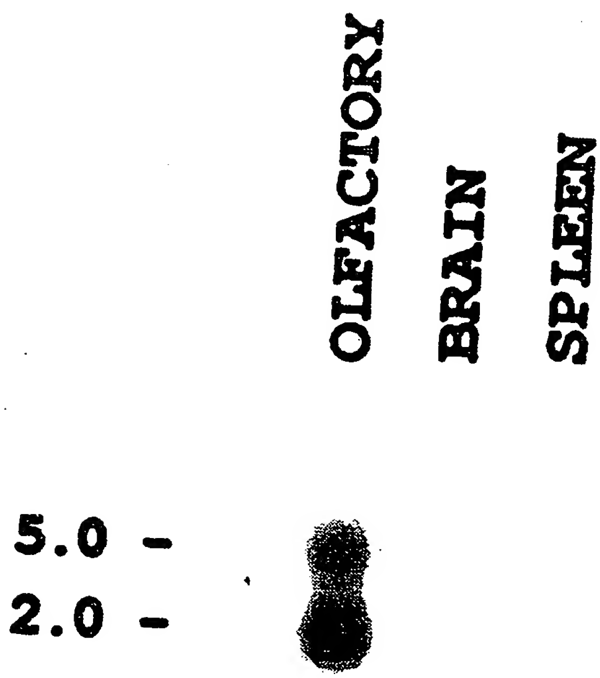


Figure 4A

F3				M	D	S	S	N	R	T	R	V	S	E	11
F5				M	S	S	T	N	Q	S	S	V	T	E	11
F6	M	A	W	S	T	G	Q	N	L	S	T	P	G	P	14
F12			M	E	S	G	N	S	T	R	R	F	S	S	12
I3				M	N	-	-	N	Q	T	F	I	T	Q	9
I7			M	E	R	R	N	H	S	G	R	V	S	E	12
I8				M	N	-	-	N	K	T	V	I	T	H	9
I8				M	T	R	R	N	Q	T	A	I	S	Q	11
I14				M	T	G	N	N	Q	T	L	I	L	E	11
I15				M	T	E	E	N	Q	T	V	I	S	Q	11

F3	F	L	L	L	G	F	V	E	N	K	D	L	Q	P	25
F5	F	L	L	L	G	L	S	R	Q	P	Q	Q	Q	Q	25
F6	F	I	L	L	G	F	P	G	P	R	S	M	R	I	28
F12	F	F	L	L	G	F	T	E	N	P	Q	L	H	F	26
I3	F	L	L	L	G	L	P	I	P	E	E	H	Q	H	23
I7	F	V	L	L	G	F	P	A	P	A	P	L	R	V	26
I8	F	L	L	L	G	L	P	I	P	P	E	H	Q	Q	23
I9	F	F	L	L	G	L	P	F	P	P	E	Y	Q	H	25
I14	F	L	L	L	G	L	P	I	P	S	E	Y	H	L	25
I15	F	L	L	L	F	L	P	I	P	S	E	H	Q	H	25

Figur 4B

	I														
F3	L	I	Y	G	L	F	L	S	N	Y	L	V	T	V	39
F5	L	L	F	L	L	F	L	I	N	Y	L	A	T	V	39
F6	G	L	F	L	L	F	L	V	N	Y	L	L	T	V	42
F12	L	I	F	A	L	F	L	S	N	Y	L	V	T	V	40
I3	L	F	Y	A	L	F	L	V	N	Y	L	T	T	I	37
I7	L	L	F	F	L	S	L	L	X	Y	V	L	V	L	40
I8	L	F	F	A	L	F	L	I	N	Y	L	T	T	F	37
I9	L	F	Y	A	L	F	L	A	N	Y	L	T	T	L	39
I14	L	F	Y	A	L	F	L	A	N	Y	L	T	I	I	29
I15	V	F	Y	A	L	F	L	S	N	Y	L	T	T	V	39

	I														
F3	I	G	N	I	S	I	I	V	A	I	I	S	D	P	53
F5	L	G	N	L	L	I	I	L	A	I	G	T	D	S	53
F6	V	G	N	L	A	I	I	S	L	V	G	A	H	R	56
F12	L	G	N	L	L	I	I	M	A	I	I	T	Q	S	54
I3	L	G	N	L	L	I	I	V	L	V	Q	L	D	S	51
I7	T	E	N	M	L	I	I	I	A	I	R	N	H	P	54
I8	L	G	N	L	L	I	V	V	L	V	Q	L	D	S	51
I9	L	G	N	L	I	I	I	I	L	I	L	L	D	S	53
I14	L	G	N	L	L	I	I	V	L	V	R	L	D	S	53
I15	L	G	N	L	I	I	I	I	L	I	H	L	D	S	53

Figur 4C

				II											
F3	C	L	H	T	P	M	Y	F	F	L	S	N	L	S	67
F5	R	L	H	T	P	M	Y	F	F	L	S	N	L	S	67
F6	C	L	Q	T	P	M	Y	F	F	L	C	N	L	S	70
F12	H	L	H	T	P	M	Y	F	F	L	A	N	L	S	68
I3	Q	L	H	T	P	M	Y	L	F	L	S	N	L	S	65
I7	T	L	H	K	P	M	Y	F	F	L	A	N	M	S	68
I8	H	L	H	T	P	M	Y	L	F	L	S	N	L	S	65
I9	H	L	H	T	P	M	Y	L	F	L	S	N	L	S	67
I14	H	L	H	M	P	M	Y	L	F	L	S	N	L	S	67
I15	H	L	H	T	P	M	Y	L	F	L	S	N	L	S	67

	II														
F3	F	V	D	I	C	F	I	S	T	T	V	P	K	M	81
F5	F	V	D	V	C	F	S	S	T	T	V	P	K	V	81
F6	F	L	E	I	W	F	T	T	A	C	V	P	K	T	84
F12	F	V	D	I	C	F	T	S	T	T	I	P	K	M	82
I3	F	S	D	L	C	F	S	S	V	T	M	P	K	L	79
I7	F	L	E	I	W	Y	V	T	V	T	I	P	K	M	82
I8	F	S	D	L	C	F	S	S	V	T	M	L	K	L	79
I9	F	A	D	L	C	F	S	S	V	T	M	P	K	L	67
I14	F	S	D	L	C	F	S	S	V	T	M	P	K	L	67
I15	F	S	D	L	C	F	S	S	V	T	M	P	K	L	67

Figure 4D

F3	**L**	-	-	-	-	-	V	**N**	I	Q	T	**Q**	N	N	V	91
F5	**L**	-	-	-	-	-	A	**N**	H	I	L	G	S	Q	A	91
F6	**L**	-	-	-	-	-	A	T	F	A	P	R	G	G	V	94
F12	**L**	-	-	-	-	-	V	N	I	Y	T	**Q**	S	K	**S**	92
I3	**L**	-	-	-	-	-	Q	N	M	R	S	**Q**	K	T	**S**	89
I7	**L**	A	G	F	I	G	S	K	E	N	H	G	Q	L		96
I8	**L**	-	-	-	-	-	Q	**N**	I	Q	S	**Q**	V	P	**S**	89
I9	**L**	-	-	-	-	-	Q	**N**	M	Q	S	**Q**	V	P	**S**	91
I14	**L**	-	-	-	-	-	Q	**N**	M	Q	S	**Q**	V	P	**S**	91
I15	**L**	-	-	-	-	-	Q	**N**	M	Q	S	**Q**	V	P	**S**	91

									III						
F3	**I**	T	**Y**	A	**G**	**C**	I	**T**	**Q**	I	**Y**	**F**	**F**	**L**	105
F5	**I**	S	F	S	**G**	**C**	**L**	**T**	**Q**	L	**Y**	**F**	L	A	105
F6	**I**	S	L	A	**G**	**C**	A	**T**	**Q**	M	**Y**	**F**	V	F	108
F12	**I**	T	**Y**	E	D	**C**	I	S	**Q**	M	C	V	**F**	**L**	106
I3	**I**	P	**Y**	G	**G**	**C**	**L**	A	**Q**	T	**Y**	**F**	**F**	M	103
I7	**I**	S	F	E	A	**C**	M	**T**	**Q**	L	**Y**	**F**	**F**	**L**	110
I8	**I**	S	**Y**	A	**G**	**C**	**L**	**T**	**Q**	I	F	F	**F**	**L**	103
I9	**I**	P	**Y**	A	**G**	**C**	**L**	A	**Q**	I	**Y**	**F**	**F**	**L**	105
I14	**I**	S	**Y**	T	**G**	**C**	**L**	**T**	**Q**	L	**Y**	**F**	**F**	M	105
I15	**I**	P	F	A	**G**	**C**	**L**	**T**	**Q**	L	**Y**	**F**	Y	**L**	105

Figure 4E

	III														
F3	L	F	V	E	L	D	N	F	L	L	T	I	M	A	119
F5	V	F	G	N	M	D	N	F	L	L	A	V	M	S	119
F6	S	L	G	C	T	E	Y	F	L	L	A	V	M	A	122
F12	V	F	A	I	L	G	N	F	L	L	A	V	M	A	120
I3	V	F	G	D	M	E	S	F	L	L	V	A	M	A	117
I7	G	L	G	C	T	E	C	V	L	L	A	V	M	A	124
I8	L	F	G	Y	L	G	N	F	L	L	V	A	M	A	117
I9	F	F	G	D	L	G	N	F	L	L	V	A	M	A	119
I14	V	F	G	D	M	E	S	F	L	L	V	V	M	A	119
I15	Y	F	A	D	L	E	S	F	L	L	V	A	M	A	119

	III														
F3	Y	D	R	Y	V	A	I	C	H	P	M	H	Y	T	133
F5	Y	D	R	F	V	A	I	C	H	P	L	H	Y	T	133
F6	Y	D	R	Y	L	A	I	C	L	P	L	R	Y	G	136
F12	Y	D	R	Y	V	A	X	C	H	P	L	C	Y	T	134
I3	Y	D	R	Y	V	A	I	C	F	P	L	H	Y	T	131
I7	Y	D	R	Y	V	A	I	C	H	P	L	H	Y	P	138
I8	Y	D	R	Y	V	A	I	C	F	P	L	H	Y	T	131
I9	Y	D	R	Y	V	A	I	C	F	P	L	H	Y	M	133
I14	Y	D	R	Y	V	A	I	C	F	P	L	R	Y	T	133
I15	Y	D	R	Y	V	A	I	C	F	P	L	H	Y	M	133

Figur 4F

	IV														
F3	V	I	M	N	Y	K	L	C	G	F	L	V	L	V	147
F5	T	K	M	T	R	Q	L	C	V	L	L	V	V	G	147
F6	G	I	M	T	P	G	L	A	M	R	L	A	L	G	150
F12	V	I	V	N	H	R	L	C	I	L	L	L	L	L	148
I3	S	I	M	S	P	K	L	C	T	C	L	V	L	L	145
I7	V	I	V	S	S	R	L	C	V	Q	M	A	A	G	152
I8	N	I	M	S	H	K	L	C	T	C	L	L	L	V	145
I9	S	I	M	S	P	K	L	C	V	S	L	V	V	L	147
I14	T	I	M	S	T	K	F	C	A	S	L	V	L	L	147
I15	S	I	M	S	P	K	L	C	V	S	L	V	V	L	147

	IV														
F3	S	W	I	V	S	V	L	H	A	L	F	Q	S	L	161
F5	S	W	V	V	A	N	M	N	C	L	L	H	I	L	161
F6	S	W	L	C	G	F	S	A	I	T	V	P	A	T	164
F12	S	W	V	I	S	I	F	H	A	F	I	Q	S	L	162
I3	L	W	M	L	T	T	S	H	A	M	M	H	T	L	159
I7	S	W	A	G	G	F	G	I	S	M	V	K	V	F	166
I8	F	W	I	M	T	S	S	H	A	M	M	H	T	L	159
I9	S	W	V	L	T	T	F	H	A	M	L	H	T	L	161
I14	L	W	M	L	T	M	T	H	A	L	L	H	T	L	161
I15	S	W	V	L	T	T	F	H	A	M	L	H	T	L	161

Figur 4G

F3	M	M	L	A	L	P	F	C	T	H	L	E	I	P	175
F5	L	M	A	R	K	S	F	C	A	D	N	M	I	P	175
F6	L	I	A	R	L	S	F	C	G	S	R	V	I	N	178
F12	I	V	L	Q	L	T	F	C	G	D	V	K	I	P	176
I3	L	A	A	R	L	S	F	C	E	N	N	V	V	L	173
I7	L	I	S	R	L	S	Y	C	G	P	N	T	I	N	180
I8	L	A	A	R	L	S	F	C	E	N	N	V	L	L	173
I9	L	M	A	R	L	S	F	C	E	D	S	V	I	P	175
I14	L	I	A	R	L	S	F	C	E	K	N	V	I	L	175
I15	L	M	A	R	L	S	F	C	A	D	N	M	I	P	175

F3	H	Y	F	C	E	P	N	Q	V	I	Q	L	T	C	189
F5	H	F	F	C	D	G	T	P	L	L	K	L	S	C	189
F6	H	F	F	C	D	I	S	P	W	I	V	L	S	C	192
F12	H	F	F	C	E	L	N	Q	L	S	Q	L	T	C	190
I3	N	F	F	C	D	L	F	V	L	L	K	L	A	C	187
I7	H	F	F	C	D	V	S	P	L	L	N	L	S	C	194
I8	N	F	F	C	D	L	F	V	L	L	K	L	A	C	187
I9	H	Y	F	C	D	M	S	T	L	L	K	V	A	C	189
I14	H	F	F	C	D	I	S	A	L	L	K	L	S	C	189
I15	H	F	F	C	D	I	S	P	L	L	K	L	S	C	189

Figure 4H

								V							
F3	S	D	A	F	L	N	D	L	V	I	Y	F	T	L	203
F5	S	D	T	H	L	N	E	L	M	I	L	T	E	G	203
F6	T	D	T	Q	V	V	E	L	V	S	F	G	I	A	206
F12	S	D	N	F	P	S	H	L	I	M	N	L	V	P	204
I3	S	D	T	Y	I	N	E	L	M	I	F	I	M	S	201
I7	T	D	M	S	T	A	E	L	T	D	F	V	L	A	208
I8	S	D	T	Y	V	N	E	L	M	I	H	I	M	G	201
I9	S	D	T	H	D	N	E	L	A	I	F	I	L	G	203
I14	S	D	I	Y	V	N	E	L	M	I	Y	I	L	G	203
I15	S	D	T	H	V	N	E	L	V	I	F	V	M	G	203

	V														
F3	V	L	L	A	T	V	P	L	A	G	I	F	Y	S	217
F5	A	V	V	M	V	T	P	F	V	C	I	L	I	S	217
F6	F	C	V	I	L	G	S	C	G	I	T	L	V	S	220
F12	V	M	L	A	A	I	S	F	S	G	I	L	Y	S	218
I3	T	L	L	I	I	I	P	F	F	L	I	V	M	S	215
I7	I	F	I	L	L	G	P	L	S	V	T	G	A	S	222
I8	V	I	I	I	V	I	P	F	V	L	I	V	I	S	215
I9	G	P	I	V	V	L	P	F	L	L	I	I	V	S	203
I14	G	L	I	I	I	I	P	F	L	L	I	V	M	S	203
I15	G	L	V	I	V	I	P	F	V	L	I	I	V	S	203

Figure 4I

	V														
F3	Y	F	K	I	V	S	S	I	C	A	I	S	S	V	231
F5	Y	I	H	I	T	C	A	V	L	R	V	S	S	P	231
F6	Y	A	Y	I	I	T	T	I	I	K	I	P	S	A	234
F12	Y	F	K	I	V	S	S	I	H	S	I	S	T	V	232
I3	Y	A	R	I	I	S	S	I	L	K	V	P	S	T	229
I7	Y	M	A	I	T	G	A	V	M	R	I	P	S	A	236
I8	Y	A	K	I	I	S	S	I	L	K	V	P	S	T	229
I9	Y	A	R	I	V	S	S	I	F	K	V	P	S	S	231
I14	Y	V	R	I	F	F	S	I	L	K	F	P	S	I	231
I15	Y	A	R	V	V	A	S	I	L	K	V	P	S	V	231

					VI										
F3	H	G	K	Y	K	A	F	S	T	C	A	S	H	L	245
F5	R	G	G	W	K	S	F	S	T	C	G	S	H	L	245
F6	R	G	R	H	R	A	F	S	T	C	S	S	H	L	248
F12	Q	G	K	Y	K	A	F	S	T	C	A	S	H	L	246
I3	Q	G	I	C	K	V	F	S	T	C	G	S	H	L	243
I7	A	G	R	H	K	A	F	S	T	C	A	S	H	L	250
I8	Q	S	I	H	K	V	F	S	T	C	G	S	H	L	243
I9	Q	S	I	H	K	A	F	S	T	C	G	S	H	L	245
I14	Q	D	I	Y	K	V	F	S	T	C	G	S	H	L	245
I15	R	G	I	H	K	I	F	S	T	C	G	S	H	L	245

Figur 4J

	VI														
F3	S	V	V	S	L	F	Y	C	T	G	L	G	V	Y	259
F5	A	V	V	C	L	F	Y	G	T	V	I	A	V	Y	259
F6	T	V	V	L	I	W	Y	G	S	T	I	F	L	H	262
F12	S	I	V	S	L	F	Y	S	T	G	L	G	V	Y	260
I3	S	V	V	S	L	F	Y	G	T	I	I	G	L	Y	257
I7	T	V	V	I	I	F	Y	A	A	S	I	F	I	Y	264
I8	S	V	V	S	L	F	Y	G	T	I	I	G	L	Y	257
I9	S	V	V	S	L	F	Y	G	T	V	I	G	L	Y	259
I14	S	V	V	T	L	F	Y	G	T	I	F	G	I	Y	259
I15	S	V	V	S	L	F	Y	G	T	I	I	G	L	Y	259

	VI												VII		
F3	L	S	S	A	A	N	N	S	S	Q	A	S	A	T	273
F5	F	N	P	S	S	S	H	L	A	G	R	D	M	A	273
F6	V	R	T	S	V	E	S	S	L	D	L	T	K	A	276
F12	V	S	S	A	V	V	Q	S	S	H	S	A	A	S	274
I3	L	C	P	A	G	N	N	S	T	V	K	E	M	V	271
I7	A	R	P	K	A	L	S	A	F	D	T	N	K	L	278
I8	L	C	P	S	G	D	N	F	S	L	K	G	S	A	271
I9	L	C	P	S	A	N	N	S	T	V	K	E	T	V	273
I14	L	C	P	S	G	N	N	S	T	V	K	E	I	A	273
I15	L	C	P	S	A	N	N	S	T	V	K	E	T	V	273

Figur 4K

VII

F3	A	S	V	M	Y	T	V	V	T	P	M	V	N	P	287
F5	A	A	V	M	Y	A	V	V	T	P	M	L	N	P	287
F6	I	T	V	L	N	T	I	V	T	P	V	L	N	P	290
F12	A	S	V	M	Y	T	V	V	T	P	M	L	N	P	288
I3	M	A	M	M	Y	T	V	V	T	P	M	L	N	P	285
I7	V	S	V	L	Y	A	V	I	V	P	L	F	N	P	292
I8	M	A	M	M	Y	T	V	V	T	P	M	L	N	P	285
I9	M	S	L	M	Y	T	M	V	T	P	M	L	N	P	287
I14	M	A	M	M	Y	T	V	V	T	P	M	L	N	P	287
I15	M	A	M	M	Y	T	V	V	T	P	M	L	N	P	287

VII

F3	F	I	Y	S	L	R	N	K	D	V	K	S	V	L	301
F5	F	I	Y	S	L	R	N	S	D	M	K	A	A	L	301
F6	F	I	Y	T	L	R	N	K	D	V	K	E	A	L	304
F12	F	I	Y	S	L	R	N	K	D	V	K	R	A	L	302
I3	F	I	Y	S	L	R	N	R	D	M	K	R	A	L	299
I7	I	I	Y	C	L	R	N	Q	D	V	K	R	A	L	306
I8	F	I	Y	S	L	R	N	R	D	M	K	Q	A	L	299
I9	F	I	Y	S	L	R	N	R	D	I	K	D	A	L	301
I14	F	I	Y	S	L	R	N	R	D	M	K	R	A	L	301
I15	F	I	Y	S	L	R	N	R	D	M	K	E	A	L	301

Figur 4L

F3	K	K	T	L	C	E	E	V	I	R	S	P	P	S	315
F5	R	K	V	L	A	M	R	F	P	S	K	Q	-		313
F6	R	R	T	V	K	G	K	-							311
F12	E	R	L	L	E	G	N	C	K	V	H	H	W	T	316
I3	I	R	V	I	C	S	M	K	I	T	L	-			310
I7	R	R	T	L	H	L	A	Q	D	Q	E	A	N	T	320
I8	I	R	V	T	C	S	K	K	I	S	L	P	W	-	312
I9	E	K	I	M	C	K	K	Q	I	P	S	F	L	-	314
I14	I	R	V	I	C	T	K	K	I	S	L	-			312
I15	I	R	V	L	C	K	K	K	I	T	F	C	L	-	314

F3	L	L	H	F	F	L	V	L	C	H	L	P	C	F	329
F5															
F6															
F12	G	-													317
I3															
I7	N	K	G	S	K	I	G	-							327
I8															
I9															
I14															
I15															

Figur 4M

F3	I F C Y -	333
F5		
F6		
F12		
I3		
I7		
I8		
I9		
I14		
I15		

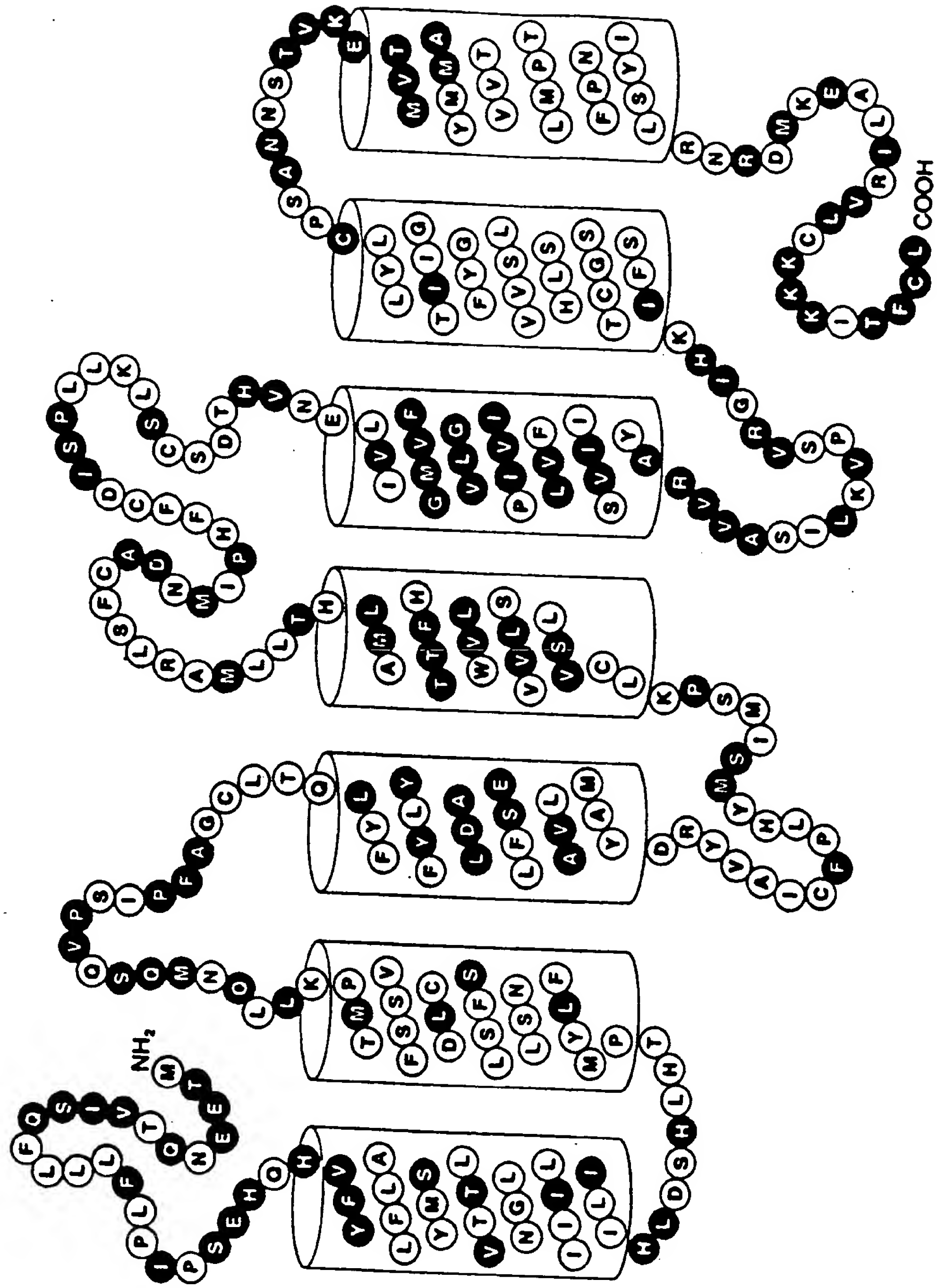


Figure 5

Figure 6A(1)

V

F2	R	V	**N**	**E**	V	V	**I**	F	I	V	V	S	L	F
F3	F	L	**N**	D	**L**	V	**I**	Y	F	T	L	V	L	L
F5	H	L	**N**	**E**	**L**	M	**I**	L	T	E	G	A	V	V
F6	Q	V	V	**E**	**L**	V	S	F	G	I	A	F	C	V
F7	H	V	**N**	**E**	**L**	V	**I**	F	V	M	G	G	I	I
F8	F	P	S	H	**L**	T	M	H	L	V	P	V	I	L
F12	F	P	S	H	**L**	I	M	N	L	V	P	V	M	L
F13	F	P	S	H	**L**	I	M	N	L	V	P	V	M	L
F23	F	**L**	N	D	V	I	M	Y	F	A	L	V	L	L
F24	H	E	I	**E**	M	I	**I**	L	V	L	A	A	F	N
I3	Y	I	**N**	**E**	**L**	M	**I**	F	I	M	S	T	L	L
I7	S	T	A	**E**	**L**	T	D	F	V	L	A	I	F	I
I8	Y	V	**N**	**E**	**L**	M	**I**	H	I	M	G	V	I	I
I9	H	D	**N**	**E**	**L**	A	**I**	F	I	L	G	G	P	I
I11	H	L	**N**	**E**	**L**	M	**I**	L	T	E	G	A	V	V
I12	F	P	S	H	**L**	I	M	N	L	V	P	V	M	L
I14	Y	V	**N**	**E**	**L**	M	**I**	Y	I	L	G	G	L	I
I15	H	V	**N**	**E**	**L**	V	**I**	F	V	M	G	G	L	V

Figure 6A(2)

	V													
F2	L	V	L	**P**	**F**	A	L	**I**	I	M	**S**	**Y**	V	R
F3	A	T	V	**P**	L	A	G	**I**	F	Y	**S**	**Y**	F	K
F5	M	V	T	**P**	**F**	V	C	**I**	L	I	**S**	**Y**	I	H
F6	I	H	G	S	C	G	I	T	L	V	**S**	**Y**	A	Y
F7	L	V	I	**P**	**F**	V	L	**I**	I	V	**S**	**Y**	V	R
F8	A	A	I	S	L	S	G	**I**	L	Y	**S**	**Y**	F	K
F12	A	A	I	S	**F**	S	G	**I**	L	Y	**S**	**Y**	F	K
F13	A	A	I	S	**F**	S	G	**I**	L	Y	**S**	**Y**	F	K
F23	A	V	V	**P**	L	L	G	**I**	L	Y	**S**	**Y**	S	K
F24	L	I	S	S	L	L	V	V	L	V	**S**	**Y**	L	F
I3	I	I	I	**P**	**F**	F	L	**I**	V	M	**S**	**Y**	A	R
I7	L	L	G	**P**	L	S	V	T	G	A	**S**	**Y**	M	A
I8	I	V	I	**P**	**F**	V	L	**I**	V	I	**S**	**Y**	A	K
I9	V	V	L	**P**	**F**	L	L	**I**	I	V	**S**	**Y**	A	R
I11	M	V	T	**P**	F	V	C	**I**	L	I	**S**	**Y**	I	H
I12	G	A	I	S	L	S	G	**I**	L	Y	**S**	**Y**	F	K
I14	I	I	I	**P**	**F**	L	L	**I**	V	M	**S**	**Y**	V	R
I15	I	V	I	**P**	**F**	V	L	**I**	I	V	**S**	**Y**	A	R

Figure 6A(3)

F2	I	V	S	S	I	L	K	V	P	S	S	Q	G	I
F3	I	V	S	S	I	C	A	I	S	S	V	H	G	K
F5	I	T	C	A	V	L	R	V	S	S	P	R	G	G
F6	I	I	T	T	I	I	K	I	P	S	A	R	G	R
F7	I	V	S	S	I	L	K	V	P	S	A	R	G	I
F8	I	V	S	S	I	R	S	M	S	S	V	Q	G	K
F12	I	V	S	S	I	H	S	I	S	T	V	Q	G	K
F13	I	V	S	S	I	R	S	V	S	S	V	K	G	K
F23	I	V	S	S	I	R	A	I	S	T	V	Q	G	K
F24	I	L	I	A	I	L	R	M	N	S	A	E	G	R
I3	I	I	S	S	I	L	K	V	P	S	T	Q	G	I
I7	I	T	G	A	V	M	R	I	P	S	A	A	G	R
I8	I	I	S	S	I	L	K	V	P	S	T	Q	S	I
I9	I	V	S	S	I	F	K	V	P	S	S	Q	S	I
I11	I	T	W	A	V	L	R	V	S	S	P	R	G	G
I12	I	V	S	S	V	R	S	I	S	S	V	Q	G	K
I14	I	F	F	S	I	L	K	F	P	S	I	Z	D	I
I15	V	V	A	S	I	L	K	V	P	S	V	R	G	I

Figure 6A(4)

F2	Y K
F3	Y K
F5	W K
F6	H R
F7	R K
F8	Y K
F12	Y K
F13	Y K
F23	Y K
F24	R K
I3	C K
I7	H K
I8	H K
I9	H K
I11	W K
I12	H K
I14	Y K
I15	H K

Figure 6B

					V									
F12	F	P	S	H	L	I	M	N	L	V	P	V	M	L
F13	F	P	S	H	L	I	M	N	L	V	P	V	M	L
F8	F	P	S	H	L	T	M	H	L	V	P	V	I	L
I12	F	P	S	H	L	I	M	N	L	V	P	V	M	L
F23	F	L	N	D	V	I	M	Y	F	A	L	V	L	L
F3	F	L	N	D	L	V	I	Y	F	T	L	V	L	L

	V													
F12	A	A	I	S	F	S	G	I	L	Y	S	Y	F	K
F13	A	A	I	S	F	S	G	I	L	Y	S	Y	F	K
F8	A	A	I	S	L	S	G	I	L	Y	S	Y	F	K
I12	G	A	I	S	L	S	G	I	L	Y	S	Y	F	K
F23	A	V	V	P	L	L	G	I	L	Y	S	Y	S	K
F3	A	T	V	P	L	A	G	I	F	Y	S	Y	F	K

Figure 6B (Continued)

F12	I	V	S	S	I	H	S	I	S	T	V	Q	G	K
F13	I	V	S	S	I	R	S	V	S	S	V	K	G	K
F8	I	V	S	S	I	R	S	M	S	S	V	Q	G	K
I12	I	V	S	S	V	R	S	I	S	S	V	Q	G	K
F23	I	V	S	S	I	R	A	I	S	T	V	Q	G	K
F3	I	V	S	S	I	C	A	I	S	S	S	H	G	K

F12	Y	K
F13	Y	K
F8	Y	K
I12	H	K
F23	Y	K
F3	Y	K

Figure 6C

F7	H	V	N	E	L	V	I	F	V	M	G	G	I	I
I15	H	V	N	E	L	V	I	F	V	M	G	G	L	V
I3	Y	I	N	E	L	M	I	F	I	M	S	T	L	L
I8	Y	V	N	E	L	M	I	H	I	M	G	V	I	I
I9	H	D	N	E	L	A	I	F	I	L	G	G	P	I
I14	Y	V	N	E	L	M	I	Y	I	L	G	G	L	I

F7	L	V	I	P	F	V	L	I	I	V	S	Y	V	R
I15	I	V	I	P	F	V	L	I	I	V	S	Y	A	R
I3	I	I	I	P	F	F	L	I	V	M	S	Y	A	R
I8	I	V	I	P	F	V	L	I	V	I	S	Y	A	K
I9	V	V	L	P	F	L	L	I	I	V	S	Y	A	R
I14	I	I	I	P	F	L	L	I	V	M	S	Y	V	R

Figure 6C (Continued)

F7	I	V	S	S	I	L	K	V	P	S	A	R	G	I
I15	V	V	A	S	I	L	K	V	P	S	V	R	G	I
I3	I	I	S	S	I	L	K	V	P	S	T	Q	G	I
I8	I	I	S	S	I	L	K	V	P	S	T	Q	S	I
I9	I	V	S	S	I	F	K	V	P	S	S	Q	S	I
I14	I	F	F	S	I	L	K	F	P	S	I	Q	D	I

F7	R	K
I15	H	K
I3	C	K
I8	H	K
I9	H	K
I14	Y	K

Figure 6D

	V
F5	H L N E L M I L T E G A V V
I11	H L N E L M I L T E G A V V
	V
F5	M V T P F V C I L I S Y I H
I11	M V T P F V C I L I S Y I H
F5	I T C A V L R V S S P R G G
I11	I T W A V L R V S S P R G G
F5	W K
I11	W K

Figure 7

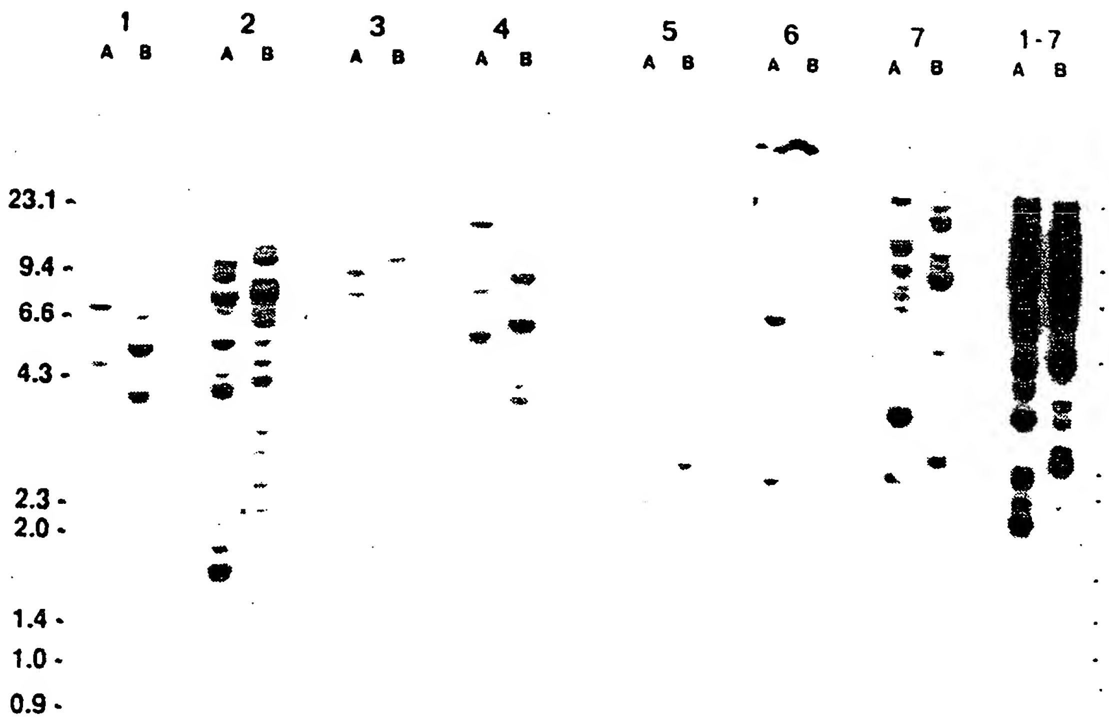


Figure 8

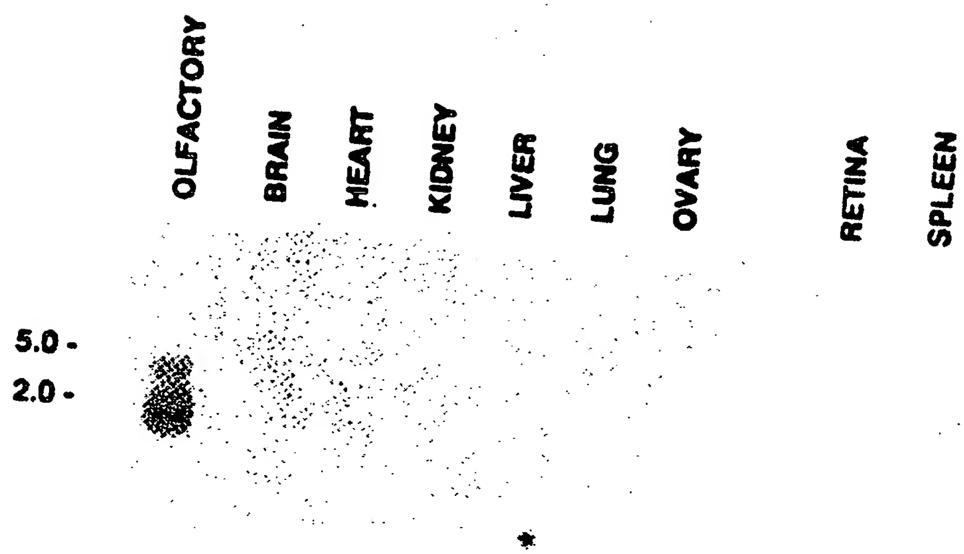

OLFACTORY
BRAIN
HEART
KIDNEY
LIVER
LUNG
OVARY
RETINA
SPLEEN
5.0 -
2.0 -

Figure 9A Translated sequence of F3T.D1S

```
           10           20           30            40           50           60
            *            *            *             *            *            *
ATG GAC TCA AGC AAC AGG ACA AGA GTT TCA GAA TTT CTT CTT CTT GGA TTT GTA GAA AAC
 M   D   S   S   N   R   T   R   V   S   E   F   L   L   L   G   F   V   E   N

           70           80           90           100          110          120
            *            *            *             *            *            *
AAA GAC CTA CAA CCC CTT ATT TAT GGT CTT TTT CTC TCT ATG TAC CTG GTT ACT GTC ATT
 K   D   L   Q   P   L   I   Y   G   L   F   L   S   M   Y   L   V   T   V   I

          130          140          150           160          170          180
            *            *            *             *            *            *
GGA AAC ATA TCC ATT ATT GTG GCT ATC ATT TCA GAT CCC TGT CTG CAC ACC CCC ATG TAT
 G   N   I   S   I   I   V   A   I   I   S   D   P   C   L   H   T   P   M   Y

          190          200          210           220          230          240
            *            *            *             *            *            *
TTC TTC CTC TCT AAC CTG TCC TTT GTG GAC ATC TGT TTC ATT TCA ACC ACT GTT CCA AAC
 F   F   L   S   N   L   S   F   V   D   I   C   F   I   S   T   T   V   P   K

          250          260          270           280          290          300
            *            *            *             *            *            *
ATG TTA GTG AAC ATC CAG ACC CAA AAC AAT GTC ATC ACC TAT GCA GGA TGC ATT ACC CAG
 M   L   V   N   I   Q   T   Q   N   N   V   I   T   Y   A   G   C   I   T   Q
```

Figure 9B

```
        310               320               330               340               350               360
          *                 *                 *                 *                 *                 *
ATA TAC TTT TTC TTG CTC TTT GTA GAA TTG GAC AAC TTC TTG CTG ACT ATC ATG GCC TAT
 I   Y   F   F   L   L   F   V   E   L   D   N   F   L   L   T   I   M   A   Y

        370               380               390               400               410               420
          *                 *                 *                 *                 *                 *
GAC CGT TAC GTA GCC ATC TGT CAC CCC ATG CAC TAC ACA GTT ATC ATG AAC TAC AAG CTC
 D   R   Y   V   A   I   C   H   P   M   H   Y   T   V   I   M   N   Y   K   L

        430               440               450               460               470               480
          *                 *                 *                 *                 *                 *
TGT GGA TTT CTG GTT CTG GTA TCT TGG ATT GTA AGT GTT CTG CAT GCC TTG TTT CAA ACC
 C   G   F   L   V   L   V   S   W   I   V   S   V   L   H   A   L   F   Q   S

        490               500               510               520               530               540
          *                 *                 *                 *                 *                 *
TTG ATG ATG TTG GCG CTG CCC TTC TGC ACA CAT CTG GAA ATC CCA CAC TAC TTC TGT GAA
 L   M   M   L   A   L   P   F   C   T   H   L   E   I   P   H   Y   F   C   E

        550               560               570               580               590               600
          *                 *                 *                 *                 *                 *
CCT AAT CAG GTG ATT CAA CTC ACC TGT TCT GAT GCA TTT CTT AAT GAT CTT GTG ATA TAT
 P   N   Q   V   I   Q   L   T   C   S   D   A   F   L   N   D   L   V   I   Y

        610               620               630               640               650               660
```

Figure 9C

```
                 *              *              *              *              *      *
TTT ACA CTT GTG CTG CTG GCT ACT GTT CCT CTT GCT GGC ATC TTC TAT TCT TAC TTC AAG
 F   T   L   V   L   L   A   T   V   P   L   A   G   I   F   Y   S   Y   F   K

            670            680            690            700            710    720
             *              *              *              *              *      *
ATA GTG TCC TCC ATA TGT GCT ATA TCG TCA GTT CAT GGG AAG TAC AAA GCA TTC TCC ACC
 I   V   S   S   I   C   A   I   S   S   V   H   G   K   Y   K   A   F   S   T

            730            740            750            760            770    780
             *              *              *              *              *      *
TGT GCA TCT CAC CTT TCA GTC GTG TCT TTA TTT TAC TGC ACA GGA CTA GGA GTG TAC CTC
 C   A   S   H   L   S   V   V   S   L   F   Y   C   T   G   L   G   V   Y   L

            790            800            810            820            830    840
             *              *              *              *              *      *
AGT TCT GCT GCA AAC AAC AGC TCA CAG GCA AGT GCC ACA GCC TCA GTC ATG TAC ACT GTA
 S   S   A   A   N   N   S   S   Q   A   S   A   T   A   S   V   M   Y   T   V

            850            860            870            880            890    900
             *              *              *              *              *      *
GTT ACC CCT ATG GTG AAC CCT TTT ATC TAT AGT CTT AGG AAT AAA GAT GTT AAG AGT GTT
    PRONUC/TRA    OPTION

 V   T   P   M   V   N   P   F   I   Y   S   L   R   N   K   D   V   K   S   V
```

Figure 9D

```
                 910            920            930            940            950            960
                  *              *              *              *              *              *
CTG AAA AAA ACT CTT TGT GAG GAA GTT ATA AGG AGT CCA CCT TCC CTA CTT CAT TTC TTC
 L   K   K   T   L   C   E   E   V   I   R   S   P   P   S   L   L   H   F   F

                 970            980            990           1000
                  *              *              *              *
CTA GTG TTA TGT CAT CTC CCT TGT TTT ATT TTT TGT TAT TAA
 L   V   L   C   H   L   P   C   F   I   F   C   Y   -
```

Translation begun with base no. 57
Translated to base no.1058
Sequence printed from base no. 57 to base no.1058
Sequence numbered beginning with base no. 57

Figure 10A Translated sequence of F5T.D1S

```
                 10                  20                  30                  40                  50                  60
                  *                   *                   *                   *                   *                   *
ATG AGC AGC ACC AAC CAG TCC AGT GTC ACC GAG TTC CTC CTC CTG GGA CTC TCC AGG CAG
 M   S   S   T   N   Q   S   S   V   T   E   F   L   L   L   G   L   S   R   Q
                 70                  80                  90                 100                 110                 120
                  *                   *                   *                   *                   *                   *
CCC CAG CAG CAG CAG CTC CTC TTC CTG CTC TTC CTC ATC ATG TAC CTG GCC ACT GTC CTG
 P   Q   Q   Q   Q   L   L   F   L   L   F   L   I   M   Y   L   A   T   V   L
                130                 140                 150                 160                 170                 180
                  *                   *                   *                   *                   *                   *
GGA AAC CTG CTC ATC ATC CTG GCT ATT GGC ACA GAC TCC CGC CTG CAC ACC CCC ATG TAC
 G   N   L   L   I   I   L   A   I   G   T   D   S   R   L   H   T   P   M   Y
                190                 200                 210                 220                 230                 240
                  *                   *                   *                   *                   *                   *
TTC TTC CTC AGT AAC CTG TCC TTT GTG GAT GTC TGC TTC TCC TCT ACC ACT GTC CCT AAA
 F   F   L   S   N   L   S   F   V   D   V   C   F   S   S   T   T   V   P   K
                250                 260                 270                 280                 290                 300
                  *                   *                   *                   *                   *                   *
CTT CTG GCC AAC CAT ATA CTT GGG AGT CAG GCC ATT TCC TTC TCT GGG TGT CTC ACC CAG
 V   L   A   N   H   I   L   G   S   Q   A   I   S   F   S   G   C   L   T   Q
```

Figure 10B

```
                310                 320                 330                 340                 350                 360
                 *                   *                   *                   *                   *                   *
CTG TAT TTT CTC GCT GTG TTT GGT AAC ATG GAC AAT TTC CTG CTG GCT GTG ATG TCC TAT
 L   Y   F   L   A   V   F   G   N   M   D   N   F   L   L   A   V   M   S   Y

                370                 380                 390                 400                 410                 420
                 *                   *                   *                   *                   *                   *
GAC CGA TTT GTG GCC ATA TGC CAC CCT TTA CAC TAC ACA ACA AAG ATG ACC CGT CAG CTC
 D   R   F   V   A   I   C   H   P   L   H   Y   T   T   K   M   T   R   Q   L

                430                 440                 450                 460                 470                 480
                 *                   *                   *                   *                   *                   *
TGT GTC CTG CTT GTT GTG GGG TCA TGG GTT GTA GCC AAC ATG AAT TGT CTG TTG CAC ATA
 C   V   L   L   V   V   G   S   W   V   V   A   N   M   N   C   L   L   H   I

                490                 500                 510                 520                 530                 540
                 *                   *                   *                   *                   *                   *
CTG CTC ATG GCT CGA CTC TCC TTC TGT GCA GAC AAC ATG ATC CCC CAC TTC TTC TGT GAT
 L   L   M   A   R   L   S   F   C   A   D   N   M   I   P   H   F   F   C   D

                550                 560                 570                 580                 590                 600
                 *                   *                   *                   *                   *                   *
GGA ACT CCC CTC CTG AAA CTC TCC TGC TCA GAC ACA CAT CTC AAT GAG CTG ATG ATT CTT
 G   T   P   L   L   K   L   S   C   S   D   T   H   L   N   E   L   M   I   L

                610                 620                 630                 640                 650                 660
```

Figure 10C

```
                *           *           *           *           *           *
ACA GAG GGA GCT GTG GTC ATG GTC ACC CCA TTT GTC TGC ATC CTC ATC TCC TAC ATC CAC
 T   E   G   A   V   V   M   V   T   P   F   V   C   I   L   I   S   Y   I   H

               670         680         690         700         710         720
                *           *           *           *           *           *
ATC ACC TGT GCT GTC CTC AGA GTC TCA TCC CCC AGG GGA GGA TGG AAA TCC TTC TCC ACC
 I   T   C   A   V   L   R   V   S   S   P   R   G   G   W   K   S   F   S   T

               730         740         750         760         770         780
                *           *           *           *           *           *
TGT GGC TCC CAC CTG GCT GTG GTC TGC CTC TTC TAT GGC ACC GTC ATC GCT GTG TAT TTC
 C   G   S   H   L   A   V   V   C   L   F   Y   G   T   V   I   A   V   Y   F

               790         800         810         820         830         840
                *           *           *           *           *           *
AAC CCA TCA TCC TCT CAC TTA GCT GGG AGG GAC ATG GCA GCT GCA GTG ATG TAT GCA GTG
    PRONUC/TRA    OPTION

 N   P   S   S   S   H   L   A   G   R   D   M   A   A   A   V   M   Y   A   V
```

Figure 10D

```
                850                 860                 870                 880                 890                 900
                 *                   *                   *                   *                   *                   *
GTG ACC CCA ATG CTG AAC CCT TTC ATC TAT AGC CTG AGG AAC AGC GAC ATG AAA GCA GCT
 V   T   P   M   L   N   P   F   I   Y   S   L   R   N   S   D   M   K   A   A

                910                 920                 930                 940
                 *                   *                   *                   *
TTA AGG AAA GTG CTC GCC ATG AGA TTT CCA TCT AAG CAG TAA
 L   R   K   V   L   A   M   R   F   P   S   K   Q   -
```

Translation begun with base no. 62
Translated to base no.1003
Sequence printed from base no. 62 to base no.1003
Sequence numbered beginning with base no. 62

Figure 11A Translated sequence of F6T.D1S

```
                 10                  20                  30                  40                  50                  60
                  *                   *                   *                   *                   *                   *
ATG GCT TGG AGT ACT GGC CAG AAC CTG TCC ACA CCA GGA CCA TTC ATC TTG CTG GGC TTC
 M   A   W   S   T   G   Q   N   L   S   T   P   G   P   F   I   L   L   G   F

                 70                  80                  90                 100                 110                 120
                  *                   *                   *                   *                   *                   *
CCA GGG CCA AGG AGC ATG CGC ATT GGG CTC TTC CTG CTT TTC CTG GTC ATG TAT CTG CTT
 P   G   P   R   S   M   R   I   G   L   F   L   L   F   L   V   M   Y   L   L

                130                 140                 150                 160                 170                 180
                  *                   *                   *                   *                   *                   *
ACG GTA GTT GGA AAC CTA GCC ATC ATC TCC CTG GTA GGT GCC CAC AGA TGC CTA CAG ACA
 T   V   V   G   N   L   A   I   I   S   L   V   G   A   H   R   C   L   Q   T

                190                 200                 210                 220                 230                 240
                  *                   *                   *                   *                   *                   *
CCC ATG TAC TTC TTC CTC TGC AAC CTC TCC TTC CTG GAG ATC TGG TTC ACC ACA GCC TGC
 P   M   Y   F   F   L   C   N   L   S   F   L   E   I   W   F   T   T   A   C

                250                 260                 270                 280                 290                 300
                  *                   *                   *                   *                   *                   *
GTA CCC AAG ACC CTG GCC ACA TTT GCG CCT CGG GGT GGA GTC ATT TCC TTG GCT GGC TGT
 V   P   K   T   L   A   T   F   A   P   R   G   G   V   I   S   L   A   G   C
```

Figure 11B

```
                 310          320          330          340          350         360
                  *            *            *            *            *           *
GCC ACA CAG ATG TAC TTT GTC TTT TCT TTG GGC TGT ACC GAG TAC TTC CTG CTG GCT GTG
 A   T   Q   M   Y   F   V   F   S   L   G   C   T   E   Y   F   L   L   A   V

                 370          380          390          400          410         420
                  *            *            *            *            *           *
ATG GCT TAT GAC CGC TAC CTG GCC ATC TGC CTG CCA CTG CGC TAT GGT GGC ATC ATG ACT
 M   A   Y   D   R   Y   L   A   I   C   L   P   L   R   Y   G   G   I   M   T

                 430          440          450          460          470         480
                  *            *            *            *            *           *
CCT GGG CTG GCG ATG CGG TTG GCC CTG GGA TCC TGG CTG TGT GGG TTT TCT GCA ATC ACA
 P   G   L   A   M   R   L   A   L   G   S   W   L   C   G   F   S   A   I   T

                 490          500          510          520          530         540
                  *            *            *            *            *           *
GTT CCT GCT ACC CTC ATT GCC CGC CTC TCT TTC TGT GGC TCA CGT GTC ATC AAC CAC TTC
 V   P   A   T   L   I   A   R   L   S   F   C   G   S   R   V   I   N   H   F

                 550          560          570          580          590         600
                  *            *            *            *            *           *
TTC TGT GAC ATT TCG CCC TGG ATA GTG CTT TCC TGC ACC GAC ACG CAG GTG GTG GAA CTG
 F   C   D   I   S   P   W   I   V   L   S   C   T   D   T   Q   V   V   E   L

                 610          620          630          640          650         660
```

Figure 11C

```
         *                  *                     *                            *                  *                 *
GTG TCC TTT GGC ATT GCC TTC TGT GTT ATT CTG GGC TCG TGT GGT ATC ACA CTA GTC TCC
 V   S   F   G   I   A   F   C   V   I   L   G   S   C   G   I   T   L   V   S

        670         680         690         700         710         720
         *           *           *           *           *           *
TAT GCT TAC ATC ATC ACT ACC ATC ATC AAG ATT CCC TCT GCC CGG GGC CGG CAC CGC GCC
 Y   A   Y   I   I   T   T   I   I   K   I   P   S   A   R   G   R   H   R   A

        730         740         750         760         770         780
         *           *           *           *           *           *
TTC TCA ACC TGC TCA TCC CAT CTC ACT GTG GTG CTG ATT TGG TAT GGC TCC ACC ATC TTC
 F   S   T   C   S   S   H   L   T   V   V   L   I   W   Y   G   S   T   I   F

        790         800         810         820         830         840
         *           *           *           *           *           *
TTG CAT GTG AGG ACC TCG GTA GAG AGC TCC TTG GAC CTC ACC AAA GCT ATC ACA GTG CTG
    PRONUC/TRA    OPTION

 L   H   V   R   T   S   V   E   S   S   L   D   L   T   K   A   I   T   V   L
```

Figure 11D

```
            850                 860                 870                     880                 890                 900
             *                   *                   *                       *                   *                   *
AAC ACC ATT GTC ACA CCT GTG CTG AAC CCT TTC ATA TAT ACT CTG AGG AAC AAG GAT GTC
 N   T   I   V   T   P   V   L   N   P   F   I   Y   T   L   R   N   K   D   V

            910                 920                 930
             *                   *                   *
AAG GAA GCT CTG CGC AGG ACG GTG AAG GGG AAG TGA
 K   E   A   L   R   R   T   V   K   G   K   -
```

Translation begun with base no. 75
Translated to base no.1010
S quence printed from base no. 75 to base no.1010
Sequence numbered beginning with base no. 75

Figure 12A Translated sequence of F12T.D1S

```
                              10                  20                  30                    40                  50                    60
                               *                   *                   *                     *                   *                     *
ATG GAA TCA GGG AAC AGC ACA AGA AGA TTT TCA AGT TTT TTT CTT CTT GGA TTT ACA GAA
 M   E   S   G   N   S   T   R   R   F   S   S   F   F   L   L   G   F   T   E
             70          80          90         100         110         120
              *           *           *           *           *           *
AAC CCA CAA CTT CAC TTC CTC ATT TTT GCA CTA TTC CTG TCC ATG TAC CTG GTA ACA GTC
 N   P   Q   L   H   F   L   I   F   A   L   F   L   S   M   Y   L   V   T   V
            130         140         150         160         170         180
              *           *           *           *           *           *
CTT GGG AAC CTG CTT ATC ATT ATG GCC ATC ATC ACA CAG TCT CAT TTG CAT ACA CCC ATG
 L   G   N   L   L   I   I   M   A   I   I   T   Q   S   H   L   H   T   P   M
            190         200         210         220         230         240
              *           *           *           *           *           *
TAC TTT TTC CTT GCT AAC CTA TCC TTT GTG GAC ATC TGT TTC ACC TCC ACC ACC ATC CCA
 Y   F   F   L   A   N   L   S   F   V   D   I   C   F   T   S   T   T   I   P
            250         260         270         280         290         300
              *           *           *           *           *           *
```

Figure 12B

```
AAG ATG TTG GTA AAT ATA TAC ACC CAG AGC AAG AGC ATC ACC TAT GAA GAC TGT ATT AGC
 K   M   L   V   N   I   Y   T   Q   S   K   S   I   T   Y   E   D   C   I   S

            310         320         330         340         350         360
             *           *           *           *           *           *
CAG ATG TGT GTC TTC TTG GTT TTC GCA GAA TTG GGC AAC TTT CTC CTG GCT GTG ATG GCC
 Q   M   C   V   F   L   V   F   A   E   L   G   N   F   L   L   A   V   M   A

            370         380         390         400         410         420
             *           *           *           *           *           *
TAT GAC CGA TAT GTG GCT A-C TGT CAC CCA CTG TGT TAC ACA GTC ATT GTG AAC CAC CGG
 Y   D   R   Y   V   A   X   C   H   P   L   C   Y   T   V   I   V   N   H   R

            430         440         450         460         470         480
             *           *           *           *           *           *
CTC TGT ATC CTG CTG CTT CTG CTG TCC TGG GTT ATC AGC ATT TTC CAT GCC TTC ATA CAG
 L   C   I   L   L   L   L   L   S   W   V   I   S   I   F   H   A   F   I   Q

            490         500         510         520         530         540
             *           *           *           *           *           *
AGC TTA ATT GTG CTA CAG TTG ACC TTC TGT GGA GAT GTG AAA ATC CCT CAC TTC TTC TGT
 S   L   I   V   L   Q   L   T   F   C   G   D   V   K   I   P   H   F   F   C

            550         560         570         580         590         600
             *           *           *           *           *           *
GAA CTT AAT CAG CTG TCC CAA CTC ACC TGT TCA GAC AAC TTT CCA AGT CAC CTC ATA ATG
 E   L   N   Q   L   S   Q   L   T   C   S   D   N   F   P   S   H   L   I   M
```

Figure 12C

```
                610                 620                 630                     640                 650                 660
                 *                   *                   *                       *                   *                   *
AAT CTT GTA CCT GTT ATG TTG GCA GCC ATT TCC TTC AGT GGC ATC CTT TAC TCT TAT TTC
 N   L   V   P   V   M   L   A   A   I   S   F   S   G   I   L   Y   S   Y   F

                670                 680                 690                     700                 710                 720
                 *                   *                   *                       *                   *                   *
AAG ATA GTA TCC TCC ATA CAT TCT ATC TCC ACA GTT CAG GGG AAG TAC AAG GCA TTT TCT
 K   I   V   S   S   I   H   S   I   S   T   V   Q   G   K   Y   K   A   F   S

                730                 740                 750                     760                 770                 780
                 *                   *                   *                       *                   *                   *
ACT TGT GCC TCT CAC CTT TCC ATT GTC TCC TTA TTT TAT AGT ACA GGC CTC GGA GTG TAC
 T   C   A   S   H   L   S   I   V   S   L   F   Y   S   T   G   L   G   V   Y

                790                 800                 810                     820                 830                 840
                 *                   *                   *                       *                   *                   *
GTC AGT TCT GCT GTG GTC CAA AGC TCA CAT TCT GCT GCA AGT GCT TCG GTC ATG TAT ACT
    PRONUC/TRA    OPTION

 V   S   S   A   V   V   Q   S   S   H   S   A   A   S   A   S   V   M   Y   T
```

Figure 12D

```
                    850              860              870                  880                  890                  900
                     *                *                *                    *                    *                    *
GTG GTC ACC CCC ATG CTG AAC CCC TTC ATT TAT AGT CTA AGG AAT AAA GAT GTG AAG AGA
 V   V   T   P   M   L   N   P   F   I   Y   S   L   R   N   K   D   V   K   R

                    910              920              930                  940                  950
                     *                *                *                    *                    *
GCT CTG GAA AGA CTG TTA GAA GGA AAC TGT AAA GTG CAT CAT TGG ACT GGA TGA
 A   L   E   R   L   L   E   G   N   C   K   V   H   H   W   T   G   -
```

Translation begun with base no. 173
Translated to base no.1126
S quence printed from base no. 173 to base no.1126
Sequence numbered beginning with base no. 173

Figure 13A   Translated sequence of   I3T.D1S

```
                10                  20                  30                  40                  50                  60
                 *                   *                   *                   *                   *                   *
ATG AAC AAT CAA ACT TTC ATC ACC CAA TTC CTT CTC CTG GGA CTG CCC ATC CCT GAA GAA
 M   N   N   Q   T   F   I   T   Q   F   L   L   L   G   L   P   I   P   E   E

                70                  80                  90                 100                 110                 120
                 *                   *                   *                   *                   *                   *
CAT CAG CAC CTG TTC TAT GCC TTG TTC CTG GTC ATG TAC CTC ACC ACC ATC TTG GGA AAC
 H   Q   H   L   F   Y   A   L   F   L   V   M   Y   L   T   T   I   L   G   N

               130                 140                 150                 160                 170                 180
                 *                   *                   *                   *                   *                   *
TTG CTA ATC ATT GTA CTT GTT CAA CTG GAC TCC CAG CTC CAC ACA CCT ATG TAT TTG TTT
 L   L   I   I   V   L   V   Q   L   D   S   Q   L   H   T   P   M   Y   L   F

               190                 200                 210                 220                 230                 240
                 *                   *                   *                   *                   *                   *
CTC AGC AAT TTG TCT TTC TCT GAT CTA TGT TTT TCC TCT GTC ACA ATG CCC AAG CTG CTG
 L   S   N   L   S   F   S   D   L   C   F   S   S   V   T   M   P   K   L   L

               250                 260                 270                 280                 290                 300
                 *                   *                   *                   *                   *                   *
CAG AAC ATG AGG AGC CAG GAC ACA TCC ATT CCC TAT GGA GGC TGC CTG GCA CAA ACA TAC
 Q   N   M   R   S   Q   D   T   S   I   P   Y   G   G   C   L   A   Q   T   Y
```

Figure 13B

```
                        310                            320                            330                            340                            350                            360
                         *                              *                              *                              *                              *                              *
TTC TTT ATG GTT TTT GGA GAT ATG GAG AGT TTC CTT CTT GTG GCC ATG GCC TAT GAC CGC
 F   F   M   V   F   G   D   M   E   S   F   L   L   V   A   M   A   Y   D   R

370 380 390 400 410 420
TAT GTG GCC ATO TGC TTC CCT CTG CAT TAC ACC AGC ATC ATG AGC CCC AAG CTC TGT ACT
 Y   V   A   I   C   F   P   L   H   Y   T   S   I   M   S   P   K   L   C   T

430 440 450 460 470 480
TGT CTA GTG CTG TTA TTG TGG ATG CTG ACG ACA TCC CAT GCC ATG ATG CAC ACA CTG CTT
 C   L   V   L   L   L   W   M   L   T   T   S   H   A   M   M   H   T   L   L

490 500 510 520 530 540
GCA GCA AGA TTG TCT TTT TGT GAG AAC AAT GTG GTC CTC AAC TTC TTC TGT GAC CTA TTT
 A   A   R   L   S   F   C   E   N   N   V   V   L   N   F   F   C   D   L   F

550 560 570 580 590 600
GTT CTC CTA AAG CTG GCC TGC TCA GAC ACT TAT ATT AAT GAG TTG ATG ATA TTT ATC ATG
 V   L   L   K   L   A   C   S   D   T   Y   I   N   E   L   M   I   F   I   M

610 620 630 640 650 660
```

Figure 13C

```
                 *                        *                          *                          *                        *                     *
AGT ACA CTC CTC ATT ATT ATT CCA TTC TTC CTC ATT GTT ATG TCC TAT GCA AGG ATC ATA
 S   T   L   L   I   I   I   P   F   F   L   I   V   M   S   Y   A   R   I   I

            670                680                 690                  700                 710                  720
             *                  *                   *                    *                   *                    *
TCC TCT ATT CTT AAG GTT CCA TCT ACC CAA GGC ATC TGC AAG GTC TTC TCT ACC TGT GGT
 S   S   I   L   K   V   P   S   T   Q   G   I   C   K   V   F   S   T   C   G

            730                740                 750                  760                 770                  780
             *                  *                   *                    *                   *
TCC CAT CTG TCT GTA GTA TCA CTG TTC TAT GGG ACA ATT ATT GGT CTC TAC TTA TGT CCA
 S   H   L   S   V   V   S   L   F   Y   G   T   I   I   G   L   Y   L   C   P
```

Figure 14A Translated sequence of I7T.D1S

```
                     10                         20                         30                         40                         50                         60
                      *                          *                          *                          *                          *                          *
ATG GAG CGA AGG AAC CAC AGT GGG AGA GTG AGT GAA TTT GTG TTG CTG GGT TTC CCA GCT
 M   E   R   R   N   H   S   G   R   V   S   E   F   V   L   L   G   F   P   A
                     70                         80                         90                        100                        110                        120
                      *                          *                          *                          *                          *                          *
CCT GCC CCA CTG CGA GTA CTA CTA TTT TTC CTT TCT CTT CTG G-C TAT GTG TTG GTG TTG
 P   A   P   L   R   V   L   L   F   F   L   S   L   L   X   Y   V   L   V   L
                    130                        140                        150                        160                        170                        180
                      *                          *                          *                          *                          *                          *
ACT GAA AAC ATG CTC ATC ATT ATA GCA ATT AGG AAC CAC CCA ACC CTC CAC AAA CCC ATC
 T   E   N   M   L   I   I   I   A   I   R   N   H   P   T   L   H   K   P   M
                    190                        200                        210                        220                        230                        240
                      *                          *                          *                          *                          *                          *
TAT TTT TTC TTG GCT AAT ATG TCA TTT CTG GAG ATT TGG TAT GTC ACT GTT ACG ATT CCT
 Y   F   F   L   A   N   M   S   F   L   E   I   W   Y   V   T   V   T   I   P
                    250                        260                        270                        280                        290                        300
                      *                          *                          *                          *                          *                          *
AAG ATG CTC GCT GGC TTC ATT GGT TCC AAG GAG AAC CAT GGA CAG CTG ATC TCC TTT GAC
 K   M   L   A   G   F   I   G   S   K   E   N   H   G   Q   L   I   S   F   E
```

Figure 14B

```
                 310                 320                 330                     340                 350                360
                  *                   *                   *                       *                   *                  *
GCA TGC ATG ACA CAA CTC TAC TTT TTC CTG GGC TTG GGT TGC ACA GAG TGT GTC CTT CTT
 A   C   M   T   Q   L   Y   F   F   L   G   L   G   C   T   E   C   V   L   L

                 370                 380                 390                     400                 410                420
                  *                   *                   *                       *                   *                  *
GCT GTG ATG GCC TAT GAC CGC TAT GTG GCT ATC TGT CAT CCA CTC CAC TAC CCC GTC ATT
 A   V   M   A   Y   D   R   Y   V   A   I   C   H   P   L   H   Y   P   V   I

                 430                 440                 450                     460                 470                480
                  *                   *                   *                       *                   *                  *
GTC AGT AGC CGG CTA TGT GTG CAG ATG GCA GCT GGA TCC TGG GCT GGA GGT TTT GGT ATC
 V   S   S   R   L   C   V   Q   M   A   A   G   S   W   A   G   G   F   G   I

                 490                 500                 510                     520                 530                540
                  *                   *                   *                       *                   *                  *
TCC ATG GTT AAA GTT TTC CTT ATT TCT CGC CTG TCT TAC TGT GGC CCC AAC ACC ATC AAC
 S   M   V   K   V   F   L   I   S   R   L   S   Y   C   G   P   N   T   I   N

                 550                 560                 570                     580                 590                600
                  *                   *                   *                       *                   *                  *
CAC TTT TTC TGT GAT GTG TCT CCA TTG CTC AAC CTG TCA TGC ACT GAC ATG TCC ACA GCA
 H   F   F   C   D   V   S   P   L   L   N   L   S   C   T   D   M   S   T   A
```

Figure 14C

```
                 610                 620                 630                 640                 650                 660
                  *                   *                   *                   *                   *                   *
GAG CTT ACA GAC TTT GTC CTG GCC ATT TTT ATT CTG CTG GGA CCG CTC TCT GTC ACT GGC
 E   L   T   D   F   V   L   A   I   F   I   L   L   G   P   L   S   V   T   G

                 670                 680                 690                 700                 710                 720
                  *                   *                   *                   *                   *                   *
GCA TCC TAC ATG GCC ATC ACA GGT GCT GTG ATG CGC ATC CCC TCA GCT GCT GGC CGC CAT
 A   S   Y   M   A   I   T   G   A   V   M   R   I   P   S   A   A   G   R   H

                 730                 740                 750                 760                 770                 780
                  *                   *                   *                   *                   *                   *
AAA GCC TTT TCA ACC TGT GCC TCC CAC CTC ACT GTT GTG ATC ATC TTC TAT GCA GCC ACT
 K   A   F   S   T   C   A   S   H   L   T   V   V   I   I   F   Y   A   A   S

                 790                 800                 810                 820                 830                 840
                  *                   *                   *                   *                   *                   *
ATT TTC ATC TAT GCC AGG CCT AAG GCA CTC TCA GCT TTT GAC ACC AAC AAG CTG GTC TCT
 I   F   I   Y   A   R   P   K   A   L   S   A   F   D   T   N   K   L   V   S

                 850                 860                 870                 880                 890                 900
                  *                   *                   *                   *                   *                   *
GTA CTC TAC GCT GTC ATT GTA CCG TTG TTC AAT CCC ATC ATC TAC TGC TTG CGC AAC CAA
    PRONUC/TRA    OPTION

 V   L   Y   A   V   I   V   P   L   F   N   P   I   I   Y   C   L   R   N   Q
```

Figure 14D

```
                910                 920                 930                 940                 950                 960
                 *                   *                   *                   *                   *                   *
GAT GTC AAA AGA GCG CTA CGT CGC ACG CTG CAC CTG GCC CAG GAC CAG GAG GCC AAT ACC
 D   V   K   R   A   L   R   R   T   L   H   L   A   Q   D   Q   E   A   N   T

                970                 980
                 *                   *
AAC AAA GGC AGC AAA ATT GGT TAG
 N   K   G   S   K   I   G   -
```

Translation begun with base no. 119
Translated to base no.1102
Sequence printed from base no. 119 to base no.1102
Sequence numbered beginning with base no. 119

Figure 15A Translated sequence of I8T.D1S

```
                 10                          20                          30                          40                          50                          60
                  *                           *                           *                           *                           *                           *
ATG AAC AAC AAA ACT GTC ATC ACC CAT TTC CTC CTC CTG GGA TTG CCC ATC CCC CCA GAG
 M   N   N   K   T   V   I   T   H   F   L   L   L   G   L   P   I   P   P   E

                 70                          80                          90                         100                         110                         120
                  *                           *                           *                           *                           *                           *
CAC CAG CAA CTG TTC TTT GCC CTG TTC CTG ATC ATG TAC CTC ACC ACC TTT CTG GGA AAC
 H   Q   Q   L   F   F   A   L   F   L   I   M   Y   L   T   T   F   L   G   N

                130                         140                         150                         160                         170                         180
                  *                           *                           *                           *                           *                           *
CTG CTA ATT GTT GTC CTT GTT CAA CTG GAC TCT CAT CTC CAC ACA CCC ATG TAC TTG TTT
 L   L   I   V   V   L   V   Q   L   D   S   H   L   H   T   P   M   Y   L   F

                190                         200                         210                         220                         230                         240
                  *                           *                           *                           *                           *                           *
CTC AGC AAC TTG TCC TTC TCT GAT CTC TGC TTT TCC TCT GTT ACA ATG CTG AAA TTG CTC
 L   S   N   L   S   F   S   D   L   C   F   S   S   V   T   M   L   K   L   L

                250                         260                         270                         280                         290                         300
                  *                           *                           *                           *                           *                           *
CAA AAT ATA CAG AGC CAA GTA CCA TCT ATA TCC TAT GCA GGA TGC CTG ACA CAG ATA TTC
 Q   N   I   Q   S   Q   V   P   S   I   S   Y   A   G   C   L   T   Q   I   F
```

Figure 15B

```
                 310                    320                    330                    340                    350                    360
                  *                      *                      *                      *                      *                      *
TTC TTT TTG TTG TTT GGC TAC CTT GGG AAT TTC CTT CTT GTA GCC ATG GCC TAT GAC CGC
 F   F   L   L   F   G   Y   L   G   N   F   L   L   V   A   M   A   Y   D   R

                 370                    380                    390                    400                    410                    420
                  *                      *                      *                      *                      *                      *
TAT GTG GCC ATC TGC TTC CCT CTG CAT TAT ACC AAC ATC ATG AGC CAT AAG CTC TGT ACT
 Y   V   A   I   C   F   P   L   H   Y   T   N   I   M   S   H   K   L   C   T

                 430                    440                    450                    460                    470                    480
                  *                      *                      *                      *                      *                      *
TGT CTC CTG CTG GTA TTT TGG ATA ATG ACA TCA TCT CAT GCC ATG ATG CAC ACC CTG CTT
 C   L   L   L   V   F   W   I   M   T   S   S   H   A   M   M   H   T   L   L

                 490                    500                    510                    520                    530                    540
                  *                      *                      *                      *                      *                      *
GCA GCA AGA TTG TCT TTT TGT GAG AAC AAT GTA CTC CTC AAC TTT TTC TGT GAC CTG TTT
 A   A   R   L   S   F   C   E   N   N   V   L   L   N   F   F   C   D   L   F

                 550                    560                    570                    580                    590                    600
                  *                      *                      *                      *                      *                      *
GTT CTC CTA AAG TTG GCC TGC TCA GAC ACT TAT GTT AAT GAG TTG ATG ATA CAT ATC ATG
 V   L   L   K   L   A   C   S   D   T   Y   V   N   E   L   M   I   H   I   M

                 610                    620                    630                    640                    650                    660
```

Figure 15C

```
                        *                     *                     *                     *                     *                     *
GGC GTG ATC ATC ATT GTT ATT CCA TTC GTG CTC ATT GTT ATA TCC TAT GCC AAG ATC ATC
 G   V   I   I   I   V   I   P   F   V   L   I   V   I   S   Y   A   K   I   I

                670                 680                 690                 700                 710                 720
                 *                   *                   *                   *                   *                   *
TCC TCC ATT CTT AAG GTT CCA TCT ACT CAA AGC ATT CAC AAG GTC TTC TCC ACT TGT GGT
 S   S   I   L   K   V   P   S   T   Q   S   I   H   K   V   F   S   T   C   G

                730                 740                 750                 760                 770                 780
                 *                   *                   *                   *                   *                   *
TCT CAT CTC TCT GTG GTG TCT CTG TTC TAC GGG ACA ATT ATT GGT CTC TAT TTA TGT CCA
 S   H   L   S   V   V   S   L   F   Y   G   T   I   I   G   L   Y   L   C   P

                790                 800                 810                 820                 830                 840
                 *                   *                   *                   *                   *                   *
TCA GGT GAT AAT TTT AGT CTA AAG GGG TCT GCC ATG GCT ATG ATG TAC ACA GTG GTA ACT
    PRONUC/TRA     OPTION

 S   G   D   N   F   S   L   K   G   S   A   M   A   M   M   Y   T   V   V   T

                850                 860                 870                 880                 890                 900
                 *                   *                   *                   *                   *                   *
CCA ATG CTG AAC CCG TTC ATC TAC AGC CTA AGA AAC AGA GAC ATG AAG CAG GCC CTA ATA
 P   M   L   N   P   F   I   Y   S   L   R   N   R   D   M   K   Q   A   L   I
```

Figure 15D

```
                 910                 920                 930             9
                  *                   *                   *
AGA GTT ACC TGT AGC AAG AAA ATC TCT CTG CCA TGG TAG
 R   V   T   C   S   K   K   I   S   L   P   W   -
```

Translation begun with base no. 57
Translated to base no. 995
Sequence printed from base no. 57 to base no. 995
Sequence numbered beginning with base no. 57

Figure 16A   Translated sequence of   I9T.D1S

10 20 30 40 50 60

ATG ACT AGA AGA AAC CAA ACT GCC ATC TCT CAG TTC TTC CTT CTG GGC CTG CCA TTC CCC
M T R R N Q T A I S Q F F L L G L P F P

70 80 90 100 110 120

GCA GAG TAC CAA CAC CTG TTC TAT GCC CTG TTC CTG GCC ATG TAC CTC ACC ACT CTC CTG
P E Y Q H L F Y A L F L A M Y L T T L L

130 140 150 160 170 180

GGG AAC CTC ATC ATC ATC ATC CTC ATT CTA CTG GAC TCC CAT CTC CAC ACA CCC ATG TAC
G N L I I I I L I L L D S H L H T P M Y

190 200 210 220 230 240

TTG TTT CTC AGC AAT TTA TCC TTT GCC GAC CTC TGT TTT TCC TCT GTC ACA ATG CCC AAG
L F L S N L S F A D L C F S S V T M P K

250 260 270 280 290 300

Figure 16B

```
             *                   *                   *                   *                   *                   *
TTG TTG CAG AAC ATG CAG AGC CAA GTT CCA TCC ATC CCC TAT GCA GGG TGC CTG GCA CAC
 L   L   Q   N   M   Q   S   Q   V   P   S   I   P   Y   A   G   C   L   A   Q
             310                 320                 330                 340                 350                 360
             *                   *                   *                   *                   *                   *
ATA TAC TTC TTT CTG TTT TTT GGA GAC CTT GGA AAC TTC CTG CTT GTG GCC ATG GCC TAT
 I   Y   F   F   L   F   F   G   D   L   G   N   F   L   L   V   A   M   A   Y
             370                 380                 390                 400                 410                 420
             *                   *                   *                   *                   *                   *
GAC CGC TAT GTG GCC ATC TGC TTC CCC CTT CAT TAC ATG AGC ATC ATG AGC CCC AAG CTC
 D   R   Y   V   A   I   C   F   P   L   H   Y   M   S   I   M   S   P   K   L
             430                 440                 450                 460                 470                 480
             *                   *                   *                   *                   *                   *
TGT GTG AGT CTG GTG GTG CTG TCC TGG GTG CTG ACT ACC TTC CAT GCC ATG CTG CAC ACC
 C   V   S   L   V   V   L   S   W   V   L   T   T   F   H   A   M   L   H   T
             490                 500                 510                 520                 530                 540
             *                   *                   *                   *                   *                   *
CTG CTC ATG GCC AGA TTG TCA TTC TGT GAG GAC AGT GTG ATC CCT CAC TAT TTC TGT GAT
 L   L   M   A   R   L   S   F   C   E   D   S   V   I   P   H   Y   F   C   D
             550                 560                 570                 580                 590                 600
             *                   *                   *                   *                   *                   *
ATG TCT ACT CTG CTG AAA GTG GCT TGT TCT GAC ACC CAT GAT AAT GAA TTA GCA ATA TTT
 M   S   T   L   L   K   V   A   C   S   D   T   H   D   N   E   L   A   I   F
```

SUBSTITUTE SHEET

Figure 16C

```
                  610                 620                 630                 640                 650                 660
                    *                   *                   *                   *                   *                   *
ATC TTA GGG GGC CCT ATA GTT GTA CTA CCT TTC CTT CTC ATC ATT GTT TCT TAT GCA AGA
 I   L   G   G   P   I   V   V   L   P   F   L   L   I   I   V   S   Y   A   R

                  670                 680                 690                 700                 710                 720
                    *                   *                   *                   *                   *                   *
ATT GTT TCC TCC ATC TTC AAG GTC CCT TCT TCT CAA AGC ATC CAT AAA GCC TTC TCC ACC
 I   V   S   S   I   F   K   V   P   S   S   Q   S   I   H   K   A   F   S   T

                  730                 740                 750                 760                 770                 780
                    *                   *                   *                   *                   *                   *
TGT GGC TCC CAC CTG TCT GTG GTG TCA CTG TTC TAT GGG ACA GTC ATT GGT CTC TAC TTA
 C   G   S   H   L   S   V   V   S   L   F   Y   G   T   V   I   G   L   Y   L

                  790                 800                 810                 820                 830                 840
                    *                   *                   *                   *                   *                   *
TGT CCT TCA GCT AAT AAC TCC ACT GTG AAG GAG ACT GTC ATG TCT TTG ATG TAC ACA ATG
    PRONUC/TRA     OPTION

 C   P   S   A   N   N   S   T   V   K   E   T   V   M   S   L   M   Y   T   M
```

Figure 16D

```
                850                 860                 870                 880                 890                 900
                 *                   *                   *                   *                   *                   *
GTG ACA CCC ATG CTG AAC CCC TTC ATC TAC AGC CTA AGA AAC AGA GAC ATA AAA GAT GCA
 V   T   P   M   L   N   P   F   I   Y   S   L   R   N   R   D   I   K   D   A

                910                 920                 930                 940
                 *                   *                   *                   *
TTA GAA AAA ATA ATG TGC AAA AAG CAA ATT CCC TCC TTT CTA TGA
 L   E   K   I   M   C   K   K   Q   I   P   S   F   L   -
```

Translation begun with base no. 200
Translated to base no.1144
Sequence printed from base no. 200 to base no.1144
Sequ nce numbered beginning with base no. 200

Figure 17A

Translated sequence of I14T.D1S

```
                 10                          20                          30                          40                          50                    60
                  *                           *                           *                           *                           *                     *
ATG ACT GGA AAT AAC CAA ACT TTG ATC TTG GAG TTC CTC CTC CTG GGT CTG CCC ATC CCA
 M   T   G   N   N   Q   T   L   I   L   E   F   L   L   L   G   L   P   I   P

                 70                          80                          90                         100                         110                   120
                  *                           *                           *                           *                           *                     *
TCA GAG TAT CAT CTC CTG TTC TAT GCC CTG TTC CTG GCC ATG TAC CTC ACC ATC ATC CTG
 S   E   Y   H   L   L   F   Y   A   L   F   L   A   M   Y   L   T   I   I   L

                130                         140                         150                         160                         170                   180
                  *                           *                           *                           *                           *                     *
GGA AAC CTG CTA ATC ATT GTC CTT GTT CGA CTG GAC TCT CAT CTC CAC ATG CCC ATG TAC
 G   N   L   L   I   I   V   L   V   R   L   D   S   H   L   H   M   P   M   Y

                190                         200                         210                         220                         230                   240
                  *                           *                           *                           *                           *                     *
TTG TTT CTC AGC AAC TTG TCC TTC TCT GAC CTC TGC TTT TCC TCT GTC ACA ATG CCC AAA
 L   F   L   S   N   L   S   F   S   D   L   C   F   S   S   V   T   M   P   K

                250                         260                         270                         280                         290                   300
                  *                           *                           *                           *                           *                     *
TTG CTT CAG AAC ATG CAG AGC CAA GTA CCA TCT ATA TCC TAT ACA GGC TGC CTG ACA CAG
 L   L   Q   N   M   Q   S   Q   V   P   S   I   S   Y   T   G   C   L   T   Q
```

Figure 17B

```
                       310                 320                 330                 340                 350                 360
                         *                   *                   *                   *                   *                   *
CTG TAC TTC TTT ATG GTT TTT GGA GAT ATG GAG AGC TTC CTT CTT GTG GTC ATG GCC TAT
 L   Y   F   F   M   V   F   G   D   M   E   S   F   L   L   V   V   M   A   Y

                       370                 380                 390                 400                 410                 420
                         *                   *                   *                   *                   *                   *
GAC CGC TAT GTG GCC ATT TGC TTT CCT TTG CGT TAC ACC ACC ATC ATG AGC ACC AAG TTC
 D   R   Y   V   A   I   C   F   P   L   R   Y   T   T   I   M   S   T   K   F

                       430                 440                 450                 460                 470                 480
                         *                   *                   *                   *                   *                   *
TGT GCT TCA CTA GTG CTA CTT CTG TGG ATG CTG ACG ATG ACC CAT GCC CTG CTG CAT ACC
 C   A   S   L   V   L   L   L   W   M   L   T   M   T   H   A   L   L   H   T

                       490                 500                 510                 520                 530                 540
                         *                   *                   *                   *                   *                   *
CTA CTC ATT GCT AGA TTG TCT TTT TGT GAG AAG AAT GTG ATT CTT CAC TTT TTC TGT GAC
 L   L   I   A   R   L   S   F   C   E   K   N   V   I   L   H   F   F   C   D

                       550                 560                 570                 580                 590                 600
                         *                   *                   *                   *                   *                   *
ATT TCT GCT CTT CTG AAG TTG TCC TGC TCA GAC ATT TAT GTT AAT GAG CTG ATG ATA TAT
 I   S   A   L   L   K   L   S   C   S   D   I   Y   V   N   E   L   M   I   Y

                       610                 620                 630                 640                 650                 660
```

Figure 17C

```
                *                           *                            *                            *                              *                        *
ATC TTG GGT GGA CTC ATC ATT ATT ATC CCA TTC CTA TTA ATT GTT ATG TCC TAT GTT ACA
 I   L   G   G   L   I   I   I   I   P   F   L   L   I   V   M   S   Y   V   R

              670                   680                 690                 700                 710                 720
                *                     *                   *                   *                   *                   *
ATT TTC TTC TCC ATT TTG AAG TTT CCA TCT ATT CAG GAC ATC TAC AAG GTA TTC TCA ACC
 I   F   F   S   I   L   K   F   P   S   I   Q   D   I   Y   K   V   F   S   T

              730                   740                 750                 760                 770                 780
                *                     *                   *                   *                   *                   *
TGT GGT TCC CAT CTG TCT GTG GTG ACC TTG TTT TAT GGG ACA ATT TTT GGT ATC TAC TTA
 C   G   S   H   L   S   V   V   T   L   F   Y   G   T   I   F   G   I   Y   L

              790                   800                 810                 820                 830                 840
                *                     *                   *                   *                   *                   *
TGT CCA TCA GGT AAT AAT TCT ACT GTG AAG GAG ATT GCC ATG GCT ATG ATG TAC ACA GTG
    PRONUC/TRA    OPTION

 C   P   S   G   N   N   S   T   V   K   E   I   A   M   A   M   M   Y   T   V

              850                   860                 870                 880                 890                 900
                *                     *                   *                   *                   *                   *
GTG ACT CCC ATG CTG AAT CCC TTC ATC TAC AGC CTG AGG AAC AGA GAC ATG AAA AGG GCC
 V   T   P   M   L   N   P   F   I   Y   S   L   R   N   R   D   M   K   R   A
```

Figure 17D

```
                 910                 920                 930            9
                  *                   *                   *
CTA ATA AGA GTT ATC TGC ACT AAG AAA ATC TCT CTG TAA
 L   I   R   V   I   C   T   K   K   I   S   L   -
```

Translation begun with base no. 64
Translated to base no.1002
Sequence printed from base no. 64 to base no.1002
Sequence numbered beginning with base no. 64

Figure 18A   Translated sequence of   I15T.D1S

```
                  10                  20                  30                  40                  50                  60
                   *                   *                   *                   *                   *                   *
ATG ACA GAA GAG AAC CAA ACT GTG ATC TCC CAG TTC CTT CTC CTT TTC CTG CCC ATC CCC
 M   T   E   E   N   Q   T   V   I   S   Q   F   L   L   L   F   L   P   I   P

                  70                  80                  90                 100                 110                 120
                   *                   *                   *                   *                   *                   *
TCA GAG CAC CAG CAC GTG TTC TAC GCC CTG TTC CTG TCC ATG TAC CTC ACC ACT GTC CTG
 S   E   H   Q   H   V   F   Y   A   L   F   L   S   M   Y   L   T   T   V   L

                 130                 140                 150                 160                 170                 180
                   *                   *                   *                   *                   *                   *
GGG AAC CTC ATC ATC ATC ATC CTC ATT CAC CTG GAC TCC CAT CTC CAC ACA CCC ATG TAC
 G   N   L   I   I   I   I   L   I   H   L   D   S   H   L   H   T   P   M   Y

                 190                 200                 210                 220                 230                 240
                   *                   *                   *                   *                   *                   *
TTG TTT CTC AGC AAC TTG TCC TTC TCT GAT CTC TGC TTT TCC TCT GTT ACG ATG CCC AAG
 L   F   L   S   N   L   S   F   S   D   L   C   F   S   S   V   T   M   P   K

                 250                 260                 270                 280                 290                 300
                   *                   *                   *                   *                   *                   *
TTG TTG CAG AAC ATG CAG AGC CAA GTT CCA TCC ATC CCC TTT GCA GGC TGC CTG ACA CAA
```

Figure 18B

```
                310         320         330         340         350         360
                 *           *           *           *           *           *
TTA TAC TTT TAC CTG TAT TTT GCA GAC CTT GAG AGC TTC CTG CTT GTG GCC ATG GCC TAT
 L   Y   F   Y   L   Y   F   A   D   L   E   S   F   L   L   V   A   M   A   Y

                370         380         390         400         410         420
                 *           *           *           *           *           *
GAC CGC TAT GTG GCC ATC TGC TTC CCC CTT CAT TAC ATG AGC ATC ATG AGC CCC AAG CTC
 D   R   Y   V   A   I   C   F   P   L   H   Y   M   S   I   M   S   P   K   L

                430         440         450         460         470         480
                 *           *           *           *           *           *
TGT GTG AGT CTG GTG GTG CTG TCC TGG GTG CTG ACC ACC TTC CAT GCC ATG CTG CAC ACC
 C   V   S   L   V   V   L   S   W   V   L   T   T   F   H   A   M   L   H   T

                490         500         510         520         530         540
                 *           *           *           *           *           *
CTG CTC ATG GCC AGA TTG TCA TTC TGT GCG GAC AAT ATG ATC CCC CAC TTT TTC TGT GAT
 L   L   M   A   R   L   S   F   C   A   D   N   M   I   P   H   F   F   C   D

                550         560         570         580         590         600
                 *           *           *           *           *           *
ATA TCT CCT TTA TTG AAA CTG TCC TGC TCT GAC ACG CAT GTT AAT GAG TTG GTG ATA TTT
 I   S   P   L   L   K   L   S   C   S   D   T   H   V   N   E   L   V   I   F

                610         620         630         640         650         660
```

Figure 18C

```
          *                   *                   *                   *                   *                   *
GTC ATG GGA GGG CTT GTT ATT GTC ATT CCA TTT GTG CTC ATC ATT GTA TCT TAT GCA CGA
 V   M   G   G   L   V   I   V   I   P   F   V   L   I   I   V   S   Y   A   R

        670         680         690         700         710         720
          *           *           *           *           *           *
GTT GTC GCC TCC ATT CTT AAA GTC CCT TCT GTC CGA GGC ATC CAC AAG ATC TTC TCC ACC
 V   V   A   S   I   L   K   V   P   S   V   R   G   I   H   K   I   F   S   T

        730         740         750         760         770         780
          *           *           *           *           *           *
TGC GGC TCC CAT CTG TCT GTG GTG TCA CTG TTC TAT GGG ACA ATC ATT GGT CTC TAC TTA
 C   G   S   H   L   S   V   V   S   L   F   Y   G   T   I   I   G   L   Y   L

        790         800         810         820         830         840
          *           *           *           *           *           *
TGT CCG TCA GCT AAT AAC TCT ACT GTG AAG GAG ACT GTC ATG GCC ATG ATG TAC ACA GTG
     PRONUC/TRA    OPTION

 C   P   S   A   N   N   S   T   V   K   E   T   V   M   A   M   M   Y   T   V

        850         860         870         880         890         900
          *           *           *           *           *           *
GTG ACC CCC ATG CTG AAC CCC TTC ATC TAC AGC CTG AGG AAC AGA GAC ATG AAA GAG GCA
 V   T   P   M   L   N   P   F   I   Y   S   L   R   N   R   D   M   K   E   A
```

Figure 18D

```
                  910                 920                 930                     940
                   *                   *                   *                       *
CTG ATA AGA GTC CTT TGT AAA AAG AAA ATT ACC TTC TGT CTA TGA
 L   I   R   V   L   C   K   K   K   I   T   F   C   L   -
```

Translation begun with base no. 8
Translated to base no. 952
Sequence printed from base no. 8 to base no. 952
Sequence numbered beginning with base no. 8

Figure 19A

Translated Sequence of H5.D1S

		10				20		
ATC	TGT	TTT	GTG	TCT	ACC	ACT	GTC	CCA
I	C	F	V	S	T	T	V	P

		70 *				80 *		
GTC	ATC	ACC	TAT	GCA	GAC	TGC	ATC	ACC
V	I	T	Y	A	D	C	I	T

		*				*		
GAC	AGC	TTA	CTC	CTG	ACT	GTG	ATG	GCC
D	S	L	L	L	T	V	M	A

		190 *				200 *		
CAC	TAC	ACA	GTC	ATT	ATG	AGC	TCC	TGG
H	Y	T	V	I	M	S	S	W

		250 *				260 *		
GTG	AGC	ATC	CTA	TAT	TCT	CTG	TTA	CAA
V	S	I	L	Y	S	L	L	Q

Figure 19B

```
30                       40                         50                      60
*                        *                          *                       *
AAG CAG CTG GTG AAC ATC CAG ACA CAG AGC AGA
 K   Q   L   V   N   I   Q   T   Q   S   R

90                      100                        110                     120
*
CAG ATG TGC TTT TTT ATA CTC TTT GTA GTG TTG
 Q   M   C   F   F   I   L   F   V   V   L

                        160                        170                     180
*                        *                          *                       *
TAT GAC CGG TTT GTG GCC ATC TGT CAC CCC CTG
 Y   D   R   F   V   A   I   C   H   P   L

210                     220                        230                     240
*                        *                          *                       *
CTC TGT GGA CTG CTG GTT CTG GTG TCC TTG ATC
 L   C   G   L   L   V   L   V   S   W   I

270                     280                        290                     300
*                        *                          *                       *
AGC ATA ATG GCA TTG CAG CTG TCC TTC TGT ACA
 S   I   M   A   L   Q   L   S   F   C   T
```

Figure 19C

```
                 310                    320                    330
                  *                      *                      *
GAA  CTG  AAA  ATC  CCT  CAA  TTT  TTC  TGT  GAA
 E    L    K    I    P    Q    F    F    C    E

                 370                    380                    390
                  *                      *                      *
GAC  ACT  TTT  ATT  AAT  GAC  ATG  ATG  ATG  AAT
 D    T    F    I    N    D    M    M    M    N

                 430                    440                    450
                  *                                             *
CTC  GCT  GGA  ATA  TTT  TAC  T--  TAC  TTT  AAG
 L    A    G    I    F    Y    X    Y    F    K

                 490                    500                    510
                  *                      *                      *
GCT  CAG  GGG  ATG  AAT  AAA  GCA  CTT  TCC  ACC
 A    Q    G    M    N    K    A    L    S    T

                 550                    560                    570
                                         *                      *
TTT  TAT  TGT  ACA  GGC  GTA  GGT  GTG  TAC  CTT
 F    Y    C    T    G    V    G    V    Y    L

                 610                    620                    630
                  *                      *                      *
AAT  GCT  GCA  GCC  TCG  GTG  ATG  TAC  ACT  GTG
 N    A    A    A    S    V    M    Y    T    V
```

Figure 19D

```
                340                         350                         360
                 *                           *                           *
CTT AAT CAG GTC ATC CAC CTT GCC TGT TCC
 L   N   Q   V   I   H   L   A   C   S

                400                         410                         420
                 *                           *                           *
TTT ACA AGT GTG CTG CTG GGT GGG GGA TGC
 F   T   S   V   L   L   G   G   G   C

                460                         470                         480
                 *                           *                           *
ATA CTT TGT TGC ATA TGT TCG ATC TCA TCA
 I   L   C   C   I   C   S   I   S   S

                520                         530                         540
                 *                           *                           *
TGT GCA TCT CAC CTC TCA GTT GTC TCC TTA
 C   A   S   H   L   S   V   V   S   L

                580                         590                         600
                 *                           *                           *
AGT TCT GCT GCA ACC CAT AAC TCA CTC TCA
 S   S   A   A   T   H   N   S   L   S

                640
                 *
GTC ACC TCC ATG CTG
 V   T   S   M   L
```

Figure 20A

J1

```
    CATCTGCTTTACTTCTGCTAGCATCCCAAAGATGCTAGTGAATATACAGACGAAGAACAA
1   ---------+---------+---------+---------+---------+---------+ 60
     I  C  F  T  S  A  S  I  P  K  M  L  V  N  I  Q  T  K  N  K  -

    GGTGATCACCTATGAAGGCTGCATCTCCCAAGTATACTTTTCATACTCTTTGGAGTTTTG
61  ---------+---------+---------+---------+---------+---------+ 120
     V  I  T  Y  E  G  C  I  S  Q  V  Y  F  S  Y  S  L  E  F  W  -

    GACAACTTTCTTCTCGACTGTGATGGCCTATGACCGATATGTGGCCATCTGTCACCCATC
121 ---------+---------+---------+---------+---------+---------+ 180
     T  T  F  F  S  T  V  M  A  Y  D  R  Y  V  A  I  C  H  P  S  -

    TXACTACACAGGTCATCATGAACCXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
181 ---------+---------+---------+---------+---------+---------+ 240
     ?  Y  T  G  H  H  E  P  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -
```

Figure 20B

```
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
241 ---------+---------+---------+---------+---------+---------+ 300
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -

    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
301 ---------+---------+---------+---------+---------+---------+ 360
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -

    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
361 ---------+---------+---------+---------+---------+---------+ 420
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -

    XXXXXXXXTTTATTCTTACTCTAAGATAGTTTCCTCCATACGAGAAATCTCATCATCACA
421 ---------+---------+---------+---------+---------+---------+ 480
     ?  ?  ?  Y  S  Y  S  K  I  V  S  S  I  R  E  I  S  S  S  Q  -

    GGGAAAGTACAAGXXATTCTCCACCTGTGCATCCCACCTCTCAGTTGTTTCATTATTCTA
481 ---------+---------+---------+---------+---------+---------+ 540
     G  K  Y  K  ?  F  S  T  C  A  S  H  L  S  V  V  S  L  F  Y  -
```

Figure 20C

```
     TTCTACACTTTTGGGTGTGTACCTTAGTTCTTCTTTTACCCAAAACTCACACTCAACTGC
541  ---------+---------+---------+---------+---------+---------+600
      S  T  L  L  G  V  Y  L  S  S  S  F  T  Q  N  S  H  S  T  A  -

     ACGGCCATCTGTTATGTACAGTGTGGTCACCCCCATGTTG
601  ---------+---------+---------+---------+ 640
      R  A  S  V  M  Y  S  V  V  T  P  M  L  -
```

J2

Figure 21A

```
    1 ACCTCCACCACCATCCCAAAGATGCTGGTAAATATACACACCCAGAGCAATACTATCACC
      ---------+---------+---------+---------+---------+---------+ 60
      T  S  T  T  I  P  K  M  L  V  N  I  H  T  Q  S  N  T  I  T  -

   61 TATGAAGACTGTATTTCCCAGATGTTTGTACTCTTGGTTTTTGGAGAACTGGACAACTTT
      ---------+---------+---------+---------+---------+---------+ 120
      Y  E  D  C  I  S  Q  M  F  V  L  L  V  F  G  E  L  D  N  F  -

  121 CTCCTGGCTGTGATGGCCTATGATCGATATGTGGCTATCTGTCACCCACTGTATTACACA
      ---------+---------+---------+---------+---------+---------+ 180
      L  L  A  V  M  A  Y  D  R  Y  V  A  I  C  H  P  L  Y  Y  T  -

  181 GTCATTGTGAACCACCGACTCTGTATCCTGCTGCTTCTGCTGTCCTGGGTTGTCAGCATT
      ---------+---------+---------+---------+---------+---------+ 240
      V  I  V  N  H  R  L  C  I  L  L  L  L  L  S  W  V  V  S  I  -

  241 TTACATGCCTTCTTACAGAGCTTAATTGTACTACAGTTGACCTTCTGTGGAGATGTGAAA
      ---------+---------+---------+---------+---------+---------+ 300
      L  H  A  F  L  Q  S  L  I  V  L  Q  L  T  F  C  G  D  V  K  -
```

Figure 21B

```
    ATCCCTCACTTCTTCTGTGAGCTCAATCAGCTGTCCCAACTCACATGTTCAGACAACTTT
301 ---------+---------+---------+---------+---------+---------+360
    I  P  H  F  F  C  E  L  N  Q  L  S  Q  L  T  C  S  D  N  F  -

    CCAAGTCACCTCACAATGCATCTTGTACCTGTTATATTTGCAGCTATTTCCCTCAGTGGT
361 ---------+---------+---------+---------+---------+---------+420
    P  S  H  L  T  M  H  L  V  P  V  I  F  A  A  I  S  L  S  G  -

    ATCCTTTACTCTTATTTCAAGATAGTGTCTTCCATACGTTCTATGTCCTCAGTTCAAGGG
421 ---------+---------+---------+---------+---------+---------+480
    I  L  Y  S  Y  F  K  I  V  S  S  I  R  S  M  S  S  V  Q  G  -

    AAGTACAAGGCATTTTCTACATGTGCCTCTCACCTTTCCATTGTCTCCTTATTTTATAGT
481 ---------+---------+---------+---------+---------+---------+540
    K  Y  K  A  F  S  T  C  A  S  H  L  S  I  V  S  L  F  Y  S  -

    ACAGGCCTCGGGGTGTACGTCAGTTCTGCTGTGATCCGAAGCTCACACTCCTCTGCAAGT
541 ---------+---------+---------+---------+---------+---------+600
    T  G  L  G  V  Y  V  S  S  A  V  I  R  S  S  H  S  S  A  S  -

    GCTTCGGTCATGTATACTGTGGTCACCCCCATGTTG
601 ---------+---------+---------+------ 636
    A  S  V  M  Y  T  V  V  T  P  M  L  -
```

Figure 22A

J4

```
      CATAGGCTATTCATCTTCTGTCACACCCAATATGCTTGTCAACTTCCTTATAAAGCAAAA
  1   ---------+---------+---------+---------+---------+---------+ 60
       I  G  Y  S  S  S  V  T  P  N  M  L  V  N  F  L  I  K  Q  N  -

      TACCATCTCATACCTTGGATGTTCTATACAGTTTGGCTCAGCTGCTTTGTTTGGCGGTCT
 61   ---------+---------+---------+---------+---------+---------+120
       T  I  S  Y  L  G  C  S  I  Q  F  G  S  A  A  L  F  G  G  L  -

      TGAATGCTTCCTTCTGGCTGCCATGGCGTATGATCGTTTTGTAGCAATCTGCAACCCACT
121   ---------+---------+---------+---------+---------+---------+180
       E  C  F  L  L  A  A  M  A  Y  D  R  F  V  A  I  C  N  P  L  -

      GCTTTATTCAACGAAAATGTCCACACAAGTCTGTGTCCAGTTGGTTGTGGCATCTTATAT
181   ---------+---------+---------+---------+---------+---------+240
       L  Y  S  T  K  M  S  T  Q  V  C  V  Q  L  V  V  G  S  Y  I  -

      AGGGGGATTTCTTAATGCCTCCTCTTTTACCCTTTCCTTTTTTTCCTTGTCCTTCTGTGG
241   ---------+---------+---------+---------+---------+---------+300
       G  G  F  L  N  A  S  S  F  T  L  S  F  F  S  L  S  F  C  G  -
```

Figure 22B

```
301 ACCAAATAGAATCAATCACTTTTACTGTGATTTTGCTCCGTTAGTAGAACTTTCTTGCTC
    ---------+---------+---------+---------+---------+---------+360
     P  N  R  I  N  H  F  Y  C  D  F  A  P  L  V  E  L  S  C  S  -

361 TGATGTCAGTGTTCCTGATGCTGTTACCTCATTTTCTGCTGCCTCAGTTACTATGCTCAC
    ---------+---------+---------+---------+---------+---------+420
     D  V  S  V  P  D  A  V  T  S  F  S  A  A  S  V  T  M  L  T  -

421 AGTGTTTATCATAGCCATCTCCTATACCTATATCCTCATCACCATCCTGAAGATGCGTTC
    ---------+---------+---------+---------+---------+---------+480
     V  F  I  I  A  I  S  Y  T  Y  I  L  I  T  I  L  K  M  R  S  -

481 CACTGAGGGTCGACAGAAAGCATTCTCTACCTGCACTTCCCACCTCACTGCAGTCACTCT
    ---------+---------+---------+---------+---------+---------+540
     T  E  G  R  Q  K  A  F  S  T  C  T  S  H  L  T  A  V  T  L  -

541 GTGCTATGGAACCATCACATTCATCTATGTGATGCCCAAGTCCAGCTACTCCACAGACCA
    ---------+---------+---------+---------+---------+---------+600
     C  Y  G  T  I  T  F  I  Y  V  M  P  K  S  S  Y  S  T  D  Q  -

601 GAACAAGGTGGTGTCTGTGTTTTATATGGTGGTGATCCCCATGTTG
    ---------+---------+---------+---------+------ 646
     N  K  V  V  S  V  F  Y  M  V  V  I  P  M  L  -
```

Figure 23A

J7

```
     CATCTGCAAGCCCCTGCACTACACCACCATCATGAATAACCGAGTGTGCACAGTTCTAGT
  1  ---------+---------+---------+---------+---------+---------+ 60
      I  C  K  P  L  H  Y  T  T  I  M  N  N  R  V  C  T  V  L  V  -

     CCTCTCCTGTTGGTTTGCTGGCCTGTTGATCATCCTCCCACCTCTTGGTCATGGCCTCCA
 61  ---------+---------+---------+---------+---------+---------+120
      L  S  C  W  F  A  G  L  L  I  I  L  P  P  L  G  H  G  L  Q  -

     GCTGGAGTTCTGTGACTCCAATGTGATTGATCATTTTGGCTGTGATGCCTCTCCAATTCT
121  ---------+---------+---------+---------+---------+---------+180
      L  E  F  C  D  S  N  V  I  D  H  F  G  C  D  A  S  P  I  L  -

     GCAGATAACCTGCTCAGACACGGTATTTATAGAGAAAATTGTCTTGGCTTTTGCCATACT
181  ---------+---------+---------+---------+---------+---------+240
      Q  I  T  C  S  D  T  V  F  I  E  K  I  V  L  A  F  A  I  L  -

     GACACTCATCATTACTCTGGTATGTGTTGTTCTCTCCTACACATACATCATCAAGACCAT
241  ---------+---------+---------+---------+---------+---------+300
```

Figure 23B

```
    TTTAAAGTTTCCTTCTGCTCAACAAAGAAAAAAGGCCTTTTCTACATGTTCTTCCCACAT
301 ---------+---------+---------+---------+---------+---------+360
     L  K  F  P  S  A  Q  Q  R  K  K  A  F  S  T  C  S  S  H  M  -

    GATTGTGGTTTCCATCACCTATGGGAGCTGTATTTTCATCTACATCAAACCTTCAGCGAA
361 ---------+---------+---------+---------+---------+---------+420
     I  V  V  S  I  T  Y  G  S  C  I  F  I  Y  I  K  P  S  A  K  -

    GGAAGGGGTAGCCATCAATAAGGTTGTATCTGTGCTCACAACATCAGTCGCCCCTTTGCT
421 ---------+---------+---------+---------+---------+---------+480
     E  G  V  A  I  N  K  V  V  S  V  L  T  T  S  V  A  P  L  L  -

     C
481  -  481
     G
```

Figure 24A

J8

```
    CATCTGCCACCCGCTCCACTACTCTCTTCTCATGAGTCCTGACAACTGTGCTGCTCTGGT
1   ---------+---------+---------+---------+---------+---------+ 60
     I  C  H  P  L  H  Y  S  L  L  M  S  P  D  N  C  A  A  L  V  -

    AACAGTCTCCTGGGTGACAGGGGTGGGCACGGGCTTCCTGCCTTCCCTCCTGATTTCTAA
61  ---------+---------+---------+---------+---------+---------+120
     T  V  S  W  V  T  G  V  G  T  G  F  L  P  S  L  L  I  S  K  -

    GTTGGACTTCTGTGGGCCCAACCGCATCAACCATTTCTTCTGTGACCTCCCTCCATTAAT
121 ---------+---------+---------+---------+---------+---------+180
     L  D  F  C  G  P  N  R  I  N  H  F  F  C  D  L  P  P  L  I  -

    CCAGCTGTCCTGCTCCAGCGTCTTTGTGACAGAAATGGCCATCTTTGTCCTGTCCATCGC
181 ---------+---------+---------+---------+---------+---------+240
     Q  L  S  C  S  S  V  F  V  T  E  M  A  I  F  V  L  S  I  A  -
```

Figure 24B

```
    TGTGCTCTGCATCTGTTTCCTCCTAACCCXXXXXTCCTACATTTTCATAGTGTCCTCCAT
241 ---------+---------+---------+---------+---------+---------+300
     V  L  C  I  C  F  L  L  T  ?  ?  S  Y  I  F  I  V  S  S  I  -

    TCTGAGAATCCCTTCCACTACCGGCAGGATGAAGACATTTTCTACATGTGGCTCCCACCT
301 ---------+---------+---------+---------+---------+---------+360
     L  R  I  P  S  T  T  G  R  M  K  T  F  S  T  C  G  S  H  L  -

    GGCCGTGGTCACCATCTACTATGGGACCATGATCTCCATGTATGTCGGCCCAAATGCGCA
361 ---------+---------+---------+---------+---------+---------+420
     A  V  V  T  I  Y  Y  G  T  M  I  S  M  Y  V  G  P  N  A  H  -

    TCTGTCCCCGGAGCTCAACAAGGTCATTTCTGTCTTCTACACTGTGATCACCCCACTACT
421 ---------+---------+---------+---------+---------+---------+480
     L  S  P  E  L  N  K  V  I  S  V  F  Y  T  V  I  T  P  L  L  -

     G
481 - 481
```

J11

Figure 25A

```
      GTCTGCTTCTCCTCCACCACTGTCCCCAAGGTACTGGCTAACCACATACTCAGTAGTCA
2     ---------+---------+---------+---------+---------+---------+ 60
       V  C  F  S  S  T  T  V  P  K  V  L  A  N  H  I  L  S  S  Q  -

      GGCCATTTCCTTCTCTGGGTGTCTAACTCAGCTGTATTTTCTCTGTGTGTCTGTGAATAT
61    ---------+---------+---------+---------+---------+---------+ 120
       A  I  S  F  S  G  C  L  T  Q  L  Y  F  L  C  V  S  V  N  M  -

      GGACAATTTCCTGCTGGCTGTGATGGCCTATGACAGATTTGTGGCCATATGCCACCCTTT
121   ---------+---------+---------+---------+---------+---------+ 180
       D  N  F  L  L  A  V  M  A  Y  D  R  F  V  A  I  C  H  P  L  -

      GTACTACACAACAAAGATGACCCACCAGCTCTGTGTCTTGCTGGTGTCTGGATCAXXXXX
181   ---------+---------+---------+---------+---------+---------+ 240
       Y  Y  T  T  K  M  T  H  Q  L  C  V  L  L  V  S  G  S  ?  ?  -

      XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
241   ---------+---------+---------+---------+---------+---------+ 300
       ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -
```

Figure 25B

```
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
301 ---------+---------+---------+---------+---------+---------+ 360
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -

    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXTGTGATCATGGTCACCCC
361 ---------+---------+---------+---------+---------+---------+ 420
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  *  S  W  S  P  H  -

    ATTTGTCTGCATCCTCATCTCTTACATCTACATCACCAATGCAGTCCTCAGAGTCTCATC
421 ---------+---------+---------+---------+---------+---------+ 480
     P  V  C  I  L  I  S  Y  I  Y  I  T  N  A  V  L  R  V  S  S  -

    CTTTAGGGGAGGATGGAAAGCCTTCTCCACCTGTGGCTCACACCTGGCTGTGGTCTGCCT
481 ---------+---------+---------+---------+---------+---------+ 540
     P  R  G  G  W  K  A  F  S  T  C  G  S  H  L  A  V  V  C  L
```

Figure 25C

```
    CTTCTATGGCACCATCATTGCTGTGTATTTCAATCCTGTATCTTCCCATTCATCTGAGAA
541 ---------+---------+---------+---------+---------+---------+600
     F  Y  G  T  I  I  A  V  Y  F  N  P  V  S  S  H  S  S  E  K  -

    GGACACTGCAGCAACTGTGCTATACACAGTGGTGACTCCCATGTTG
601 ---------+---------+---------+---------+------ 646
     D  T  A  A  T  V  L  Y  T  V  V  T  P  M  L  -
```

J14

Figure 26A

```
    TGTCTGCTTCTCCTCCACCACTGTCCCCAAGGTACTGGCTAACCACATACTCAGTAGTCA
  1 ---------+---------+---------+---------+---------+---------+ 60
     V  C  F  S  S  T  T  V  P  K  V  L  A  N  H  I  L  S  S  Q  -

    GGCCATTTCCTTCTCTGGCTGTCTAACTCAGCTGTATTTTCTCTGTGTGTCTGTGAATAT
 61 ---------+---------+---------+---------+---------+---------+120
     A  I  S  P  S  G  C  L  T  Q  L  Y  F  L  C  V  S  V  N  M

    GGACAATTTCCTGCTGGCTGTGATGGCCTATGACAGATTTGTGGCCATATGCCACCCTTT
121 ---------+---------+---------+---------+---------+---------+180
     D  N  F  L  L  A  V  M  A  Y  D  R  F  V  A  I  C  H  P  L  -

    GTACTACACAACAAAGATGACCCACCAGCTCTGTGTCTTGCTGGTGTCTGGATCAXXXXX
181 ---------+---------+---------+---------+---------+---------+240
     Y  Y  T  T  K  M  T  H  Q  L  C  V  L  L  V  S  G  S  ?  ?

    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
241 ---------+---------+---------+---------+---------+---------+300
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?
```

Figure 26B

```
    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
301 ---------+---------+---------+---------+---------+---------+360
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -

    XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXTGTGATCATGGTCACCCC
361 ---------+---------+---------+---------+---------+---------+420
     ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  V  I  M  V  T  P  -

    ATTTGTCTGCATCCTCATCTCTTACATCTACATCACCAATGCAGTCCTCAGAGTCTCATC
421 ---------+---------+---------+---------+---------+---------+480
     F  V  C  I  L  I  S  Y  I  Y  I  T  N  A  V  L  R  V  S  S  -

    CTTTAGGGGAGGATGGAAAGCCTTCTCCACCTGTGGCTCACACCTGGCTGTGGTCTGCCT
481 ---------+---------+---------+---------+---------+---------+540
     F  R  G  G  W  K  A  F  S  T  C  G  S  H  L  A  V  V  C  L  -

    CTTCTATGGCACCATCATTGCTGTGTATTTCAATCCTGTATCTTCCCATTCATCTGAGAA
541 ---------+---------+---------+---------+---------+---------+600
     F  Y  G  T  I  I  A  V  Y  F  N  P  V  S  S  H  S  S  E  K  -

    GGACACTGCAGCAACTGTGCTATACACAGTGGTGACTCCCATGTTG
601 ---------+---------+---------+---------+------ 646
     D  T  A  A  T  V  L  Y  T  V  V  T  P  M  L  -
```

J15

Figure 27A

```
     TATCTGCAACCCTCTGCGCTACCCAGTGCTCATGAGCGGCCGGGTGTGCCTGCTCATGCT
  1  ---------+---------+---------+---------+---------+---------+ 60
      I  C  N  P  L  R  Y  P  V  L  M  S  G  R  V  C  L  L  M  V

     CGTGGCCTCCTGGTTGGGAGGATCCCTCAACGCCTCCATTCAGACTTCTCTGACCCTTCA
 61  ---------+---------+---------+---------+---------+---------+120
      V  A  S  W  L  G  G  S  L  N  A  S  I  Q  T  S  L  T  L  Q  -

     GTTCCCCTACTGTGGATCACGGAAGATCTCCCACTTCTTCTGTGAGGTGCCCTCGCTGCT
121  ---------+---------+---------+---------+---------+---------+180
      F  P  Y  C  G  S  R  K  I  S  H  F  F  C  E  V  P  S  L  L  -

     GAXXXTGGCCTGTGCAGACACTGAAGCCTATGAGCAGGTACTATTTGTGACAGGCGTGGT
181  ---------+---------+---------+---------+---------+---------+240
      ?  ?  A  C  A  D  T  E  A  Y  E  Q  V  L  F  V  T  G  V  V  -
```

Figure 27B

```
     GGTCCTCCTGGTGCCCATTACATTCATTACTGCCTCTTATGCCCTCATCCTGGCTGCTGT
241  ---------+---------+---------+---------+---------+---------+
      V  L  L  V  P  I  T  P  I  T  A  S  Y  A  L  I  L  A  A  V

     GCTCCGAATGCACTCTGCGGAGGGGAGTCAGAAGGCCCTAGCCACATGCTCCTCTCACCT
301  ---------+---------+---------+---------+---------+---------+360
      L  R  M  H  S  A  E  G  S  Q  K  A  L  A  T  C  S  S  H  L  -

     GACAGTCGTCAATCTCTTCTATGGGCCCCTTGTCTACACCTACATGTTACCTGCTTCCTA
361  ---------+---------+---------+---------+---------+---------+420
      T  V  V  N  L  F  Y  G  P  L  V  Y  T  Y  M  L  P  A  S  Y  -

     TCACTCACCAGGCCAAGACGACATAGTATCCGTCTTTTACACCGTTCTCACACCCATGCT
421  ---------+---------+---------+---------+---------+---------+480
      H  S  P  C  Q  D  D  I  V  S  V  F  Y  T  V  L  T  P  M  L  -

     T
481  - 481
     A
```

Figure 28A

J16

```
    CATCTGTAGGCCTCTTCACTATCCTACCCTCATGACCCAGACACTGTGTGCCAAGATTGC
  1 ---------+---------+---------+---------+---------+---------+ 60
     I  C  R  P  L  H  Y  P  T  L  M  T  Q  T  L  C  A  K  I  A  -

    CACTGGTTGCTGGTTGGAGGCTTGGCTGGGCCAGTGGTAGAAATTTCCTTGGTGTCTCG
 61 ---------+---------+---------+---------+---------+---------+120
     T  G  C  W  L  G  G  L  A  G  P  V  V  E  I  S  L  V  S  R  -

    TCTCCTTTTTTGTGGCCCCAATCACATTCAACACATCTTTTGTGATTTCCCACCTGTGCT
121 ---------+---------+---------+---------+---------+---------+180
     L  L  F  C  G  P  N  H  I  Q  H  I  F  C  D  F  P  P  V  L  -

    GAGCTTGGCTTGTACTGATACATCAGTGAATGTCCTGGTAGATTTTATTATAAACCTCTG
181 ---------+---------+---------+---------+---------+---------+240
     S  L  A  C  T  D  T  S  V  N  V  L  V  D  F  I  I  N  L  C  -

    CAAGATCCTGGCCACCTTCCTGCTGATCCTGAGCTCCTACTTGCAGATAATCCGCACAGT
241 ---------+---------+---------+---------+---------+---------+300
     K  I  L  A  T  F  L  L  I  L  S  S  Y  L  Q  I  I  R  T  V  -
```

Figure 28B

```
     GAGCTTGGCTTGTACTGATACATCAGTGAATGTCCTGGTAGATTTTATTATAAACCTCTG
181  ---------+---------+---------+---------+---------+---------+240
      S  L  A  C  T  D  T  S  V  N  V  L  V  D  F  I  I  N  L  C  -

     CAAGATCCTGGCCACCTTCCTGCTGATCCTGAGCTCCTACTTGCAGATAATCCGCACAGT
241  ---------+---------+---------+---------+---------+---------+300
      K  I  L  A  T  F  L  L  I  L  S  S  Y  L  Q  I  I  R  T  V  -

     GCTCAAGATTCCTTCAGCTGCAGGCAAGAAGAAAGCATTCTCGACTTGTGCCTCCCATCT
301  ---------+---------+---------+---------+---------+---------+360
      L  K  I  P  S  A  A  G  K  K  K  A  F  S  T  C  A  S  H  L  -

     CACTGTGGTTCTCATCTTCTATGGGAGCATCCTTTTCATGTATGTGCGGCTGAAGAAGAC
361  ---------+---------+---------+---------+---------+---------+420
      T  V  V  L  I  F  Y  G  S  I  L  F  M  Y  V  R  L  K  K  S  -

     TTACTCCCTTGACTACGACAGAGCCTTGGCAGTAGTCTACTCCGTGGTTACCCCTTTCCT
421  ---------+---------+---------+---------+---------+---------+480
      Y  S  L  D  Y  D  R  A  L  A  V  V  Y  S  V  V  T  P  F  L  -

     G
481  - 481
```

J17

Figure 29A

```
      AATCTGCAACCCACTGCTTTATTCCACCAAAATGTCCACACAAGTCTGTATCCAGTTGGT
  1   ---------+---------+---------+---------+---------+---------+ 60
      I  C  N  P  L  L  Y  S  T  K  M  S  T  Q  V  C  I  Q  L  V  -

      TGCAGGATCTTATATAGGGGGTTTTCTTAATACTTGCCTCATCATGTTTTACTTTTTCTC
 61   ---------+---------+---------+---------+---------+---------+120
      A  G  S  Y  I  G  G  P  L  N  T  C  L  I  M  F  Y  F  F  S  -

      TTTTCTCTTCTGTGGGCCAAATATAGTTGATCATTTTTTCTGTGATTTTGCTCCTTTXXT
121   ---------+---------+---------+---------+---------+---------+180
      F  L  P  C  G  P  N  I  V  D  H  F  F  C  D  F  A  P  ?  ?  -

      GGAACTTTCGTGCTCTGATGTGAGTGTCTCTGTAGTTGTTATGTCATTTTCTGCTGGCTC
181   ---------+---------+---------+---------+---------+---------+240
      E  L  S  C  S  D  V  S  V  S  V  V  V  M  S  F  S  A  G  S  -

      AGTTACTATGATCACAGTGTTTATCATAGCCATCTCCTATTCTTACATCCTCATCACCAT
241   ---------+---------+---------+---------+---------+---------+300
      V  T  M  I  T  V  F  I  I  A  I  S  Y  S  Y  I  L  I  T  I  -
```

Figure 29B

```
    CCTGAAGATGTCCTCAACTGAGGGCCGTCACAAGGCTTTCTCCACATGTACCTCCCACCT
301 ---------+---------+---------+---------+---------+---------+360
    L  K  M  S  S  T  E  G  R  H  K  A  F  S  T  C  T  S  H  L  -

    CACTGCAGTCACTCTCTACTATGGCACCATTACCTTCATTTATGTGATGCCCAAGTCCAC
361 ---------+---------+---------+---------+---------+---------+420
    T  A  V  T  L  Y  Y  G  T  I  T  F  I  Y  V  M  P  K  S  T  -

    ATACTCTACAGACCAGAACAAGGTGGTGTCTGTGTTTTACATGGTGGTGATCCCAATGTT
421 ---------+---------+---------+---------+---------+---------+480
    Y  S  T  D  Q  N  K  V  V  S  V  F  Y  M  V  V  I  P  M  L  -

    G
481 - 481
```

J19

Figure 30A

```
  1 TATCTGCCACCCTCTGAAGTACACAGTTATCATGAATCACTATTTTTGTGTGATGCTGCT
    ---------+---------+---------+---------+---------+---------+ 60
     I  C  H  P  L  K  Y  T  V  I  M  N  H  Y  F  C  V  M  L  L  -

 61 GCTCTTCTCTGTGTTCGTTAGCATTGCACATGCGTTCTTCCACATTTTAATGGTGTTGAT
    ---------+---------+---------+---------+---------+---------+120
     L  F  S  V  F  V  S  I  A  H  A  L  F  H  I  L  M  V  L  I  -

121 ACTGACTTTCAGCACAAAAACTGAAATCCCTCACTTTTTCTGTGAGCTGGCTCATATCAT
    ---------+---------+---------+---------+---------+---------+180
     L  T  F  S  T  K  T  E  I  P  H  F  F  C  E  L  A  H  I  I  -

181 CAAACTTACCTGTTCCGATAATTTTATCAACTATCTGCTGATATACACAGAGTCTGTCTT
    ---------+---------+---------+---------+---------+---------+240
     K  L  T  C  S  D  N  F  I  N  Y  L  L  I  Y  T  E  S  V  L  -

241 ATTTTTTGGTGTTCATATTGTAGGGATCATTTTGTCTTATATTTACACTGTATCCTCAGT
    ---------+---------+---------+---------+---------+---------+300
     F  F  G  V  H  I  V  G  I  I  L  S  Y  I  Y  T  V  S  S  V  -
```

Figure 30B

```
    TTTAAGAATGTCATTATTGGGAGGAATGTATAAAGCCTTTTCAACATGTGGATCTCATTT
301 ---------+---------+---------+---------+---------+---------+360
     L  R  M  S  L  L  G  G  M  Y  K  A  F  S  T  C  G  S  H  L  -

    GTCGGTTGTCTCTGTTTTATGGCACAGGTTTTGGGGTACACATAAGCTCTCCACTTACTG
361 ---------+---------+---------+---------+---------+---------+420
     S  V  V  S  V  L  W  H  R  F  W  G  T  H  K  L  S  T  Y  *  -

    ACTCTCCAAGGAAGACTGTAGTGGCTTCAGTGATGTACACTGTGGTTACTCAGATGCTG
421 ---------+---------+---------+---------+---------+--------- 479
     L  S  K  E  D  C  S  G  F  S  D  V  H  C  G  Y  S  D  A  -
```

Figure 31A

J20

```
    AATCTGCTACCCACTGAGGTACCTTCTCATCATGAGCTGGGTGGTGTGCACAGCACTGTC
  1 ---------+---------+---------+---------+---------+---------+ 60
    I  C  Y  P  L  R  Y  L  L  I  M  S  W  V  V  C  T  A  L  S  -

    CGTGGCAATCTGGGTCATAGGCTTTTGTGCCTCCGTTATACCTCTCTGCTTCACGATCCT
 61 ---------+---------+---------+---------+---------+---------+120
    V  A  I  W  V  I  G  F  C  A  S  V  I  P  L  C  F  T  I  L  -

    CCCACTCTGTGGTCCTTACGTCGTTGATTATCTTTTCTGCGAGCTGCCCATCCTTCTGCA
121 ---------+---------+---------+---------+---------+---------+180
    P  L  C  G  P  Y  V  V  D  Y  L  F  C  E  L  P  I  L  L  H  -

    CCTGTTCTGCACAGATACATCTCTGCTGGAGXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
181 ---------+---------+---------+---------+---------+---------+240
    L  F  C  T  D  T  S  L  L  B  ?  ?  ?  ?  ?  ?  ?  ?  ?  ?  -

    XXXXXXXXXXXXCCCTTCCTCCTGATTGTTCTCTCCTACCTTCGCATCCTGGTGGCTGTG
241 ---------+---------+---------+---------+---------+---------+300
    ?  ?  ?  ?  P  F  L  L  I  V  L  S  Y  L  R  I  L  V  A  V
```

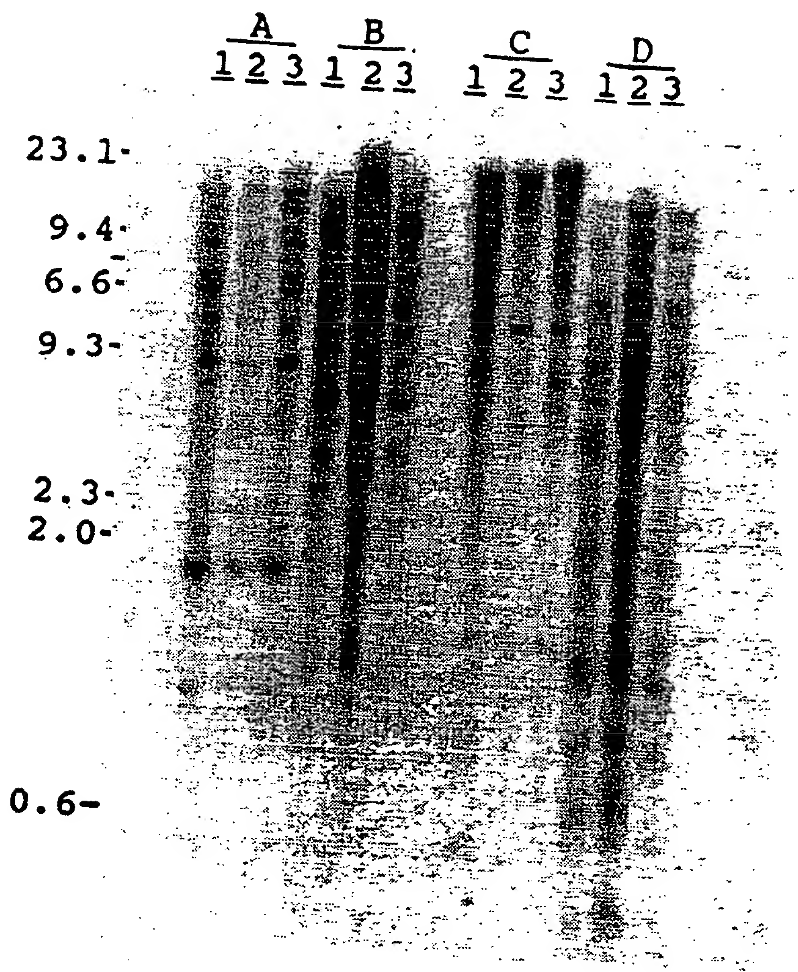
Figure 31B

```
    ATAAGAATAGACTCAGCTGAGGGCAGAAAAAAGGCCTTTTCAACTTGTGCTTCACACTTG
301 ---------+---------+---------+---------+---------+---------+360
    I  R  I  D  S  A  E  G  R  K  K  A  F  S  T  C  A  S  H  L

    GCTGTGGTGACCATCTACTATGGAACAGGGCTGATCAGGTACTTGAGGCCCAAGTCCCTT
361 ---------+---------+---------+---------+---------+---------+420
    A  V  V  T  I  Y  Y  G  T  G  L  I  R  Y  L  R  P  K  S  L

    TATTCCGCTGAGGGAGACAGACTGATCTCTGTGTTCTATGCAGTCATTGGCCCTGCACTG
421 ---------+---------+---------+---------+---------+---------+480
    Y  S  A  E  G  D  R  L  I  S  V  F  Y  A  V  I  G  P  A  L
```

Figur 32



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/02741

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C12N 15/12, 15/63, 15/64, 5/10; C07K 13/00; A01N 33/00; A61K 37/00
US CL :536/27; 424/418; 435/7.21, 172.3, 240.1, 320.1; 514/2; 530/395
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/27; 424/418; 435/7.21, 172.3 240.1, 320.1; 514/2; 530/395

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, MEDLINE, UEMBL, GENBANK, PIR, SWISS PROT, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P Y,P	Molecular Brain Research, Volume 13, No. 1-2, issued March 1992, L. A. Selbie et al., "Novel G protein-coupled receptors: a gene family of putative human olfactory receptor sequences," abstract.	1-32 33-98
Y X	Sensory Sist., Volume 1, No. 1, issued 1987, V. I. Novoselov et al., "The properties of receptor molecules from rat olfactory epithelium," abstract.	1-34, 65-98 35-64
X,P Y,P	Nature, Volume 355, issued 30 January 1992, M. Parmentier et al., "Expression of members of the putative olfactory receptor gene family in mammalian germ cells," pages 453-455, see entire document.	1-32 33-98
Y X	Biochimica Biophysica Acta, Volume 839, No. 3, issued 1985, E. E. Fesenko et al., "Molecular mechanisms of olfactory reception. VI Kinetic characteristics of camphor interaction with binding sites of rat olfactory epithelium," abstract.	1-34, 65-98 35-64

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
25 June 1992

Date of mailing of the international search report
23 July 1992

Name and mailing address of the ISA/
Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/02741

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P Y,P	Chemtracts: Organic Chemistry, Volume 4, No. 4, issued 1991, K. Touhara et al., "A novel multigene family may encode odorant receptors: a molecular basis for odor recognition," abstract.	1-32 33-98
Y,P	Chemical Senses, Volume 16, No. 5, issued 1991, R. H. R. Anholt, "Odor recognition and olfactory tranduction: the new frontier," abstract.	1-98
Y	Trends in Neuroscience, Volume 14, No. 7, issued 1991, S. Firestein, "A noseful of odor receptors," abstract.	1-98
Y	Proceedings of the National Academy of Sciences, Volume 86, issued November 1989, E. Dancigier et al., "Olfactory marker protein gene: Its structure and olfactory neuron-specific expression in transgenic mice," pages 8565-8569, see entire document.	1-34
Y	Kagaky Kogyo, Volume 40, No. 11, issued 1989, M. Kashiwayanagi et al., "High sensitivity odor sensor using artificial membrane," abstract.	1-98